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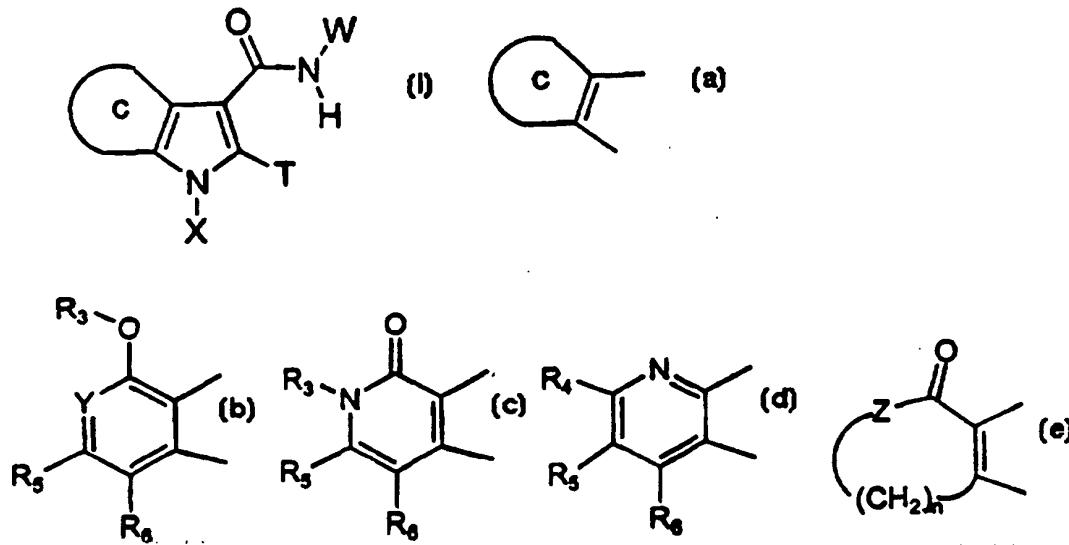
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(54) Title: CERTAIN FUSED PYRROLECARBOXANILIDES; A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS



(57) Abstract

The present invention encompasses structures of formula (I) or the pharmaceutically acceptable non-toxic salts thereof wherein (a) represents (b) or (c) or (d) or (e) wherein: W represents substituted or unsubstituted phenyl; X is hydrogen, hydroxy or lower alkyl; T is hydrogen, halogen, hydroxy, nitro, amino or alkyl; R₃ is hydrogen or an organic group; R₄ is hydrogen or substituted or unsubstituted organic substituent; R₅ and R₆ represent organic, and inorganic substituents; and n is 1, 2, 3, or 4, which compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

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Certain Fused Pyrrolecarboxanilides; A New Class of GABA Brain Receptor Ligands

Field of the Invention

This invention relates to certain fused pyrrolecarboxanilides which selectively bind to GABA_A receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating anxiety, sleep and seizure disorders, and overdoses of benzodiazepine-type drugs, and enhancing alertness. The interaction of fused pyrrolecarboxanilides of the invention with a GABA binding site, the benzodiazepine (BDZ) receptor, is described. This interaction results in the pharmacological activities of these compounds.

Description of the Related Art

γ -Aminobutyric acid (GABA) is regarded as one of the major inhibitory amino acid transmitters in the mammalian brain. Over 30 years have elapsed since its presence in the brain was demonstrated (Roberts & Frankel, J. Biol. Chem. 187: 55-63, 1950; Udenfriend, J. Biol. Chem. 187: 65-69, 1950). Since that time, an enormous amount of effort has been devoted to implicating GABA in the etiology of seizure disorders, sleep, anxiety and cognition (Tallman and Gallagher, Ann. Rev. Neuroscience 8: 21-44, 1985). Widely, although unequally, distributed through the mammalian brain, GABA is said to be a transmitter at approximately 30% of the synapses in the brain. In most regions of the brain, GABA is associated with local inhibitory neurons and only in two regions is GABA associated with longer projections. GABA mediates many of its actions through a complex of proteins localized both on cell bodies and nerve endings; these are called GABA_A receptors. Postsynaptic responses to GABA are mediated through alterations in chloride conductance that generally, although not invariably, lead to hyperpolarization of the cell. Recent investigations have indicated that the complex of proteins associated with postsynaptic GABA responses is a major site of action for a number of structurally unrelated compounds capable

of modifying postsynaptic responses to GABA. Depending on the mode of interaction, these compounds are capable of producing a spectrum of activities (either sedative, anxiolytic, and anticonvulsant, or wakefulness, seizures, and anxiety).

1,4-Benzodiazepines continue to be among the most widely used drugs in the world.
5 Principal among the benzodiazepines marketed are chlordiazepoxide, diazepam, flurazepam, and triazolam. These compounds are widely used as anxiolytics, sedative-hypnotics, muscle relaxants, and anticonvulsants. A number of these compounds are extremely potent drugs; such potency indicates a site of action with a high affinity and specificity for individual receptors. Early electrophysiological studies indicated that a major action of benzodiazepines
10 was enhancement of GABAergic inhibition. The benzodiazepines were capable of enhancing presynaptic inhibition of a monosynaptic ventral root reflex, a GABA-mediated event (Schmidt et al., 1967, Arch. Exp. Path. Pharmakol. 258: 69-82). All subsequent electrophysiological studies (reviewed in Tallman et al. 1980, Science 207: 274-81, Haefley et
15 al., 1981, Handb. Exptl. Pharmacol. 33: 95-102) have generally confirmed this finding, and by the mid-1970s, there was a general consensus among electrophysiologists that the benzodiazepines could enhance the actions of GABA.

With the discovery of the "receptor" for the benzodiazepines and the subsequent definition of the nature of the interaction between GABA and the benzodiazepines, it appears that the behaviorally important interactions of the benzodiazepines with different
20 neurotransmitter systems are due in a large part to the enhanced ability of GABA itself to modify these systems. Each modified system, in turn, may be associated with the expression of a behavior.

Studies on the mechanistic nature of these interactions depended on the demonstration of a high-affinity benzodiazepine binding site (receptor). Such a receptor is present in the
25 CNS of all vertebrates phylogenetically newer than the boney fishes (Squires & Braestrup 1977, Nature 166: 732-34, Mohler & Okada, 1977, Science 198: 854-51, Mohler & Okada, 1977, Br. J. Psychiatry 133: 261-68). By using tritiated diazepam, and a variety of other compounds, it has been demonstrated that these benzodiazepine binding sites fulfill many of the criteria of pharmacological receptors; binding to these sites in vitro is rapid, reversible,
30 stereospecific, and saturable. More importantly, highly significant correlations have been shown between the ability of benzodiazepines to displace diazepam from its binding site and activity in a number of animal behavioral tests predictive of benzodiazepine potency (Braestrup & Squires 1978, Br. J. Psychiatry 133: 249-60, Mohler & Okada, 1977, Science 198: 854-51, Mohler & Okada, 1977, Br. J. Psychiatry 133: 261-68). The average therapeutic

doses of these drugs in man also correlate with receptor potency (Tallman et al. 1980, *Science* 207: 274-281).

In 1978, it became clear that GABA and related analogs could interact at the low affinity (1 mM) GABA binding site to enhance the binding of benzodiazepines to the clonazepam-sensitive site (Tallman et al. 1978, *Nature*, 274: 383-85). This enhancement was caused by an increase in the affinity of the benzodiazepine binding site due to occupancy of the GABA site. The data were interpreted to mean that both GABA and benzodiazepine sites were allosterically linked in the membrane as part of a complex of proteins. For a number of GABA analogs, the ability to enhance diazepam binding by 50% of maximum and the ability to inhibit the binding of GABA to brain membranes by 50% could be directly correlated. Enhancement of benzodiazepine binding by GABA agonists is blocked by the GABA receptor antagonist (+) bicuculline; the stereoisomer (-) bicuculline is much less active (Tallman et al., 1978, *Nature*, 274: 383-85).

Soon after the discovery of high affinity binding sites for the benzodiazepines, it was discovered that a triazolopyridazine could interact with benzodiazepine receptors in a number of regions of the brain in a manner consistent with receptor heterogeneity or negative cooperativity. In these studies, Hill coefficients significantly less than one were observed in a number of brain regions, including cortex, hippocampus, and striatum. In cerebellum, triazolopyridazine interacted with benzodiazepine sites with a Hill coefficient of 1 (Squires et al., 1979, *Pharma. Biochem. Behav.* 10: 825-30, Klepner et al. 1979, *Pharmacol. Biochem. Behav.* 11: 457-62). Thus, multiple benzodiazepine receptors were predicted in the cortex, hippocampus, striatum, but not in the cerebellum.

Based on these studies, extensive receptor autoradiographic localization studies were carried out at a light microscopic level. Although receptor heterogeneity has been demonstrated (Young & Kuhar 1980, *J. Pharmacol. Exp. Ther.* 212: 337-46, Young et al., 1981 *J. Pharmacol Exp. Ther.* 216: 425-430, Niehoff et al. 1982, *J. Pharmacol. Exp. Ther.* 221: 670-75), no simple correlation between localization of receptor subtypes and the behaviors associated with the region has emerged from the early studies. In addition, in the cerebellum, where one receptor was predicted from binding studies, autoradiography revealed heterogeneity of receptors (Niehoff et al., 1982, *J. Pharmacol. Exp. Ther.* 221: 670-75).

A physical basis for the differences in drug specificity for the two apparent subtypes of benzodiazepine sites has been demonstrated by Sieghart & Karobath, 1980, *Nature* 286: 285-87. Using gel electrophoresis in the presence of sodium dodecyl sulfate, the presence of several molecular weight receptors for the benzodiazepines has been reported. The receptors

were identified by the covalent incorporation of radioactive flunitrazepam, a benzodiazepine which can covalently label all receptor types. The major labeled bands have molecular weights of 50,000 to 53,000, 55,000, and 57,000 and the triazolopyridazines inhibit labeling of the slightly higher molecular weight forms (53,000, 55,000, 57,000) (Seighart et al. 1983, 5 Eur. J. Pharmacol. 88: 291-99).

At that time, the possibility was raised that the multiple forms of the receptor represent "isoreceptors" or multiple allelic forms of the receptor (Tallman & Gallagher 1985, Ann. Rev. Neurosci. 8, 21-44). Although common for enzymes, genetically distinct forms of receptors have not generally been described. As we begin to study receptors using specific radioactive probes and electrophoretic techniques, it is almost certain that isoreceptors will emerge as 10 important in investigations of the etiology of psychiatric disorders in people.

The GABAa receptor subunits have been cloned from bovine and human cDNA libraries (Schoenfield et al., 1988; Duman et al., 1989). A number of distinct cDNAs were identified as subunits of the GABAa receptor complex by cloning and expression. These are 15 categorized into α , β , γ , δ , ϵ , and provide a molecular basis for the GABAa receptor heterogeneity and distinctive regional pharmacology (Shivvers et al., 1980; Levitan et al., 1989). The γ subunit appears to enable drugs like benzodiazepines to modify the GABA responses (Pritchett et al., 1989). The presence of low Hill coefficients in the binding of ligands to the GABAa receptor indicates unique profiles of subtype specific pharmacological 20 action.

Drugs that interact at the GABAa receptor can possess a spectrum of pharmacological activities depending on their abilities to modify the actions of GABA. For example, the beta-carbolines were first isolated based upon their ability to inhibit competitively the binding of diazepam to its binding site (Nielsen et al., 1979, Life Sci. 25: 679-86). The receptor binding assay is not totally predictive about the biological activity of such compounds; agonists, 25 partial agonists, inverse agonists, and antagonists can inhibit binding. When the beta-caroline structure was determined, it was possible to synthesize a number of analogs and test these compounds behaviorally. It was immediately realized that the beta-carbolines could antagonize the actions of diazepam behaviorally (Tenen & Hirsch, 1980, Nature 288: 609-10). In addition to this antagonism, beta-carbolines possess intrinsic activity of their own opposite 30 to that of the benzodiazepines; they become known as inverse agonists.

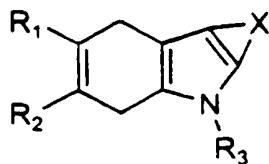
In addition, a number of other specific antagonists of the benzodiazepine receptor were developed based on their ability to inhibit the binding of benzodiazepines. The best studied of

these compounds is an imidazodiazepine (Hunkeler et al., 1981, *Nature* 290: 514-516). This compound is a high affinity competitive inhibitor of benzodiazepine and beta-carboline binding and is capable of blocking the pharmacological actions of both these classes of compounds. By itself, it possesses little intrinsic pharmacological activity in animals and humans (Hunkeler et al., 1981, *Nature* 290: 514-16; Darragh et al., 1983, *Eur. J. Clin. Pharmacol.* 14: 569-70). When a radiolabeled form of this compound was studied (Mohler & Richards, 1981, *Nature* 294: 763-65), it was demonstrated that this compound would interact with the same number of sites as the benzodiazepines and beta-carbolines, and that the interactions of these compounds were purely competitive. This compound is the ligand of choice for binding to GABAa receptors because it does not possess receptor subtype specificity and measures each state of the receptor.

The study of the interactions of a wide variety of compounds similar to the above has led to the categorizing of these compounds. Presently, those compounds possessing activity similar to the benzodiazepines are called agonists. Compounds possessing activity opposite to benzodiazepines are called inverse agonists, and the compounds blocking both types of activity have been termed antagonists. This categorization has been developed to emphasize the fact that a wide variety of compounds can produce a spectrum of pharmacological effects, to indicate that compounds can interact at the same receptor to produce opposite effects, and to indicate that beta-carbolines and antagonists with intrinsic anxiogenic effects are not synonymous.

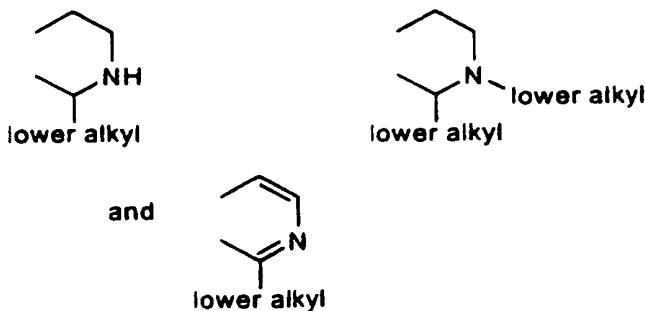
A biochemical test for the pharmacological and behavioral properties of compounds that interact with the benzodiazepine receptor continues to emphasize the interaction with the GABAergic system. In contrast to the benzodiazepines, which show an increase in their affinity due to GABA (Tallman et al., 1978, *Nature* 274: 383-85, Tallman et al., 1980, *Science* 207: 274-81), compounds with antagonist properties show little GABA shift (i.e., change in receptor affinity due to GABA) (Mohler & Richards 1981, *Nature* 294: 763-65), and the inverse agonists actually show a decrease in affinity due to GABA (Braestrup & Nielson 1981, *Nature* 294: 472-474). Thus, the GABA shift predicts generally the expected behavioral properties of the compounds.

Various compounds have been prepared as benzodiazepine agonists and antagonists. For Example, U.S. Patents Nos. 3,455,943, 4,435,403, 4,596,808, 4,623,649, and 4,719,210, German Patent No. DE 3,246,932, and Liebigs Ann. Chem. 1986, 1749 teach assorted benzodiazepine agonists and antagonists and related anti-depressant and central nervous system active compounds. U.S. Patent No. 3,455,943 discloses compounds of the formula:



wherein R₁ is a member of the group consisting of hydrogen and lower alkoxy; R₂ is a member of the group consisting of hydrogen and lower alkoxy; R₃ is a member of the group consisting of hydrogen and lower alkyl; and X is a divalent radical selected from the group consisting of

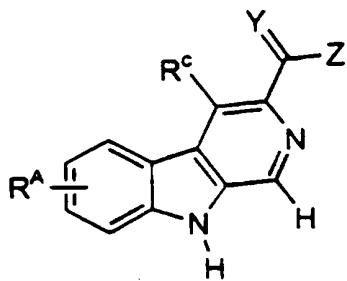
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and the non-toxic acid addition salts thereof.

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U.S. Patent No. 4,435,403 teaches compounds of the formula:



wherein

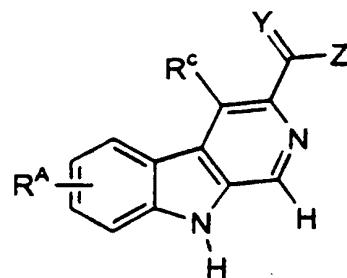
R^C is hydrogen, lower alkyl, alkoxyalkyl of up to 6 C-atoms, cycloalkyl of 3-6 C-atoms, arylalkyl of up to 8 C-atoms, or (CH₂)_nOR₁₈ wherein R₁₈ is alkyl of up to 6 C-atoms,

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cycloalkyl of 3-6 C-atoms or arylalkyl of up to 8 C-atoms and n is an integer of 1 to 3; Y is oxygen, two hydrogen atoms or NOR₁, wherein R₁ is hydrogen, lower alkyl, aryl or arylalkyl of up to 6 C-atoms, COR₂, wherein R₂ is lower alkyl of up to 6 C-atoms, or Y is CHCOOR₃, wherein R₃ is hydrogen or lower alkyl or Y is NNR₄R₅, wherein R₄ and R₅ can be the same or different and each is hydrogen, lower alkyl, C₆-10-aryl, C₇-10-arylalkyl or CONR₆R₇.

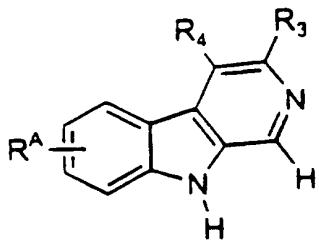
wherein R₆ and R₇ can be the same or different and each is hydrogen or lower alkyl, or R₄ and R₅ together with the connecting N-atom, form a 5- or 6-membered heterocyclic ring which optionally may also contain an O-atom or up to 3 N-atoms and which optionally may be substituted by a lower alkyl group; Z is hydrogen, or alkoxy or aralkoxy each of up to 10 C-atoms and each optionally substituted by hydroxy, or Z is alkyl of up to 6 C-atoms, C₆-10-aryl or C₇-10-arylalkyl each of which may optionally be substituted by a COOR₈ or a CONR₉R₁₀ group, wherein R₈ is alkyl of up to 6 C-atoms, and R₉ and R₁₀ can be the same or different and each is hydrogen or alkyl of up to 6 C-atoms; or Z is NR₉R₁₀, wherein R₉ and R₁₀ are as defined above; or Z is NR₁₁CHR₁₂R₁₃, wherein R₁₁ and R₁₂ each is 5
hydrogen or together form a N=C double bond, wherein R₁₃ is C₁-10-alkyl or NR₁₄R₁₅, where R₁₄ and R₁₅ are the same or different and each is hydrogen, OH or alkyl or alkoxy each of up to 6 C-atoms, or wherein R₁₂ and R₁₃ together are oxygen, in which case, R₁₁ is 10
hydrogen; or Z is COOR₂ wherein R₂ is as defined above; or Y and Z, together with the connecting C-atom, may form a 5- or 6-membered heterocyclic ring which contains an O-atom, adjoining O- and N-atoms or up to 4 N atoms and which optionally may be substituted 15
by a lower alkyl group, hydroxy or oxo.

U.S. Patent No. 4,596,808 discloses compounds of the formula:

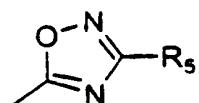


20 wherein R^A is H, F, Cl, Br, I, NO₂, CN, CH₃, CF₃, SCH₃, NR₁₆R₁₇ or NHCOR₁₆, wherein R₁₆ or R₁₇ are the same or different and each is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 C-atoms, arylalkyl or cycloalkyl each of up to 10 C-atoms, or wherein R₁₆ and R₁₇ together form a saturated or unsaturated 3-7 membered heterocyclic ring.

25 U.S. Patent No. 4,623,649 teaches compounds of the formula:



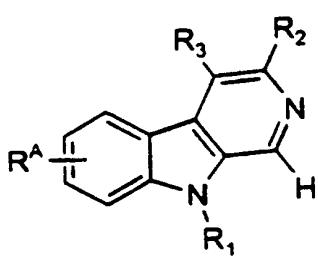
wherein R₃ is an oxadiazolyl residue of the formula



wherein R₅ stands for lower alkyl of up to 3 carbon atoms or an ester -CO₂R₆ with R₆ being
5 hydrogen or lower alkyl of up to 3 carbon atoms, R₄ is hydrogen, lower alkyl of up to 3 carbon atoms, or CH₂OR₉ wherein R₉ is lower alkyl of up to 3 carbon atoms, R^A is phenyl or a hydrocarbon residue containing 2-10 carbon atoms which can be cyclic or acyclic, saturated or unsaturated, branched or unbranched, and which can optionally be substituted by oxo, formyl OH, O-alkyl of up to 3 carbon atoms or phenyl, and wherein in a cyclic hydrocarbon residue, a CH₂-group can be replaced by oxygen.

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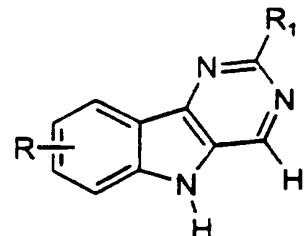
U.S. Patent No. 4,719,210 discloses compounds of the formula:



wherein R₁ is hydrogen or a protecting group, R₂ is -CH=CR₄ or -C=CR₄, R₄ is hydrogen or halogen, R₃ is hydrogen, lower alkyl or lower alkoxyalkyl, R^A is, *inter alia*, hydrogen, OR₇, lower alkyl, which optionally is substituted with aryl, lower alkoxy or NR₅R₆, R₅ and R₆ can be the same or different and in each case is hydrogen, lower alkyl or together with the nitrogen atom a 5-6 member ring, which can contain another heteroatom. R₇ is lower alkyl, optionally substituted aryl or arylalkyl, and each compound can contain one or more R^A radicals which are not hydrogen.

δ

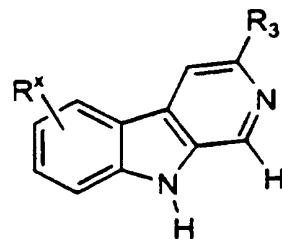
German Patent No. DE 3,246,932 discloses compounds of the formula:



wherein

5 R = halogen, NO₂, CO₂H, modified CO₂H, R₂O, R₂S(O)_n; n = 0-2; and R₁ = H, alkyl, cycloalkyl, arylalkyl, aryl, CO₂H, amino, R₂O, R₂S(O)_n.

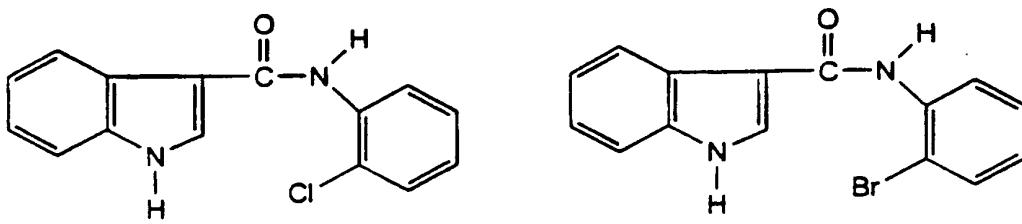
Liebigs Ann. Chem. 1986, 1749-1764 teaches compounds of the formula:



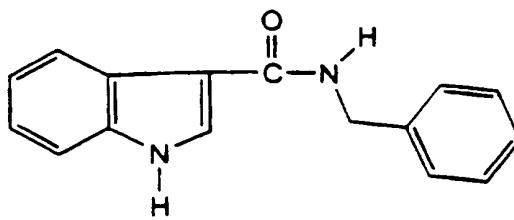
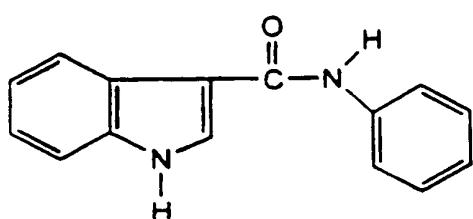
10 where R^X is hydrogen, methyl, benzyloxy, or methoxy, and R₃ is carboethoxy.

None of these compounds are indole-3-carboxamides and no such compounds displaying activity at GABA receptors have been described.

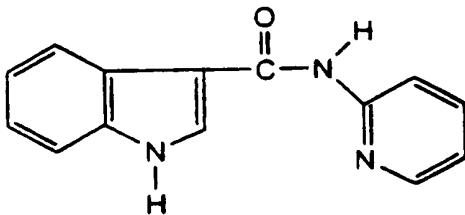
A variety of indole-3-carboxamides are described in the literature. For example, J. Org. Chem., 42: 1883-1885 (1977) discloses the following compounds.



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J. Heterocyclic Chem., 14: 519-520 (1977) discloses a compound of the following formula:



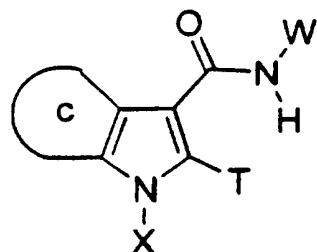
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None of these indole-3-carboxamides includes an oxy substituent at the 4-position of the indole ring.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABA_A binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

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or the pharmaceutically acceptable non-toxic salts thereof wherein:

T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;

X is hydrogen, hydroxyl or lower alkyl;

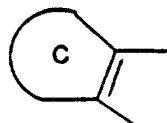
W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups

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independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having

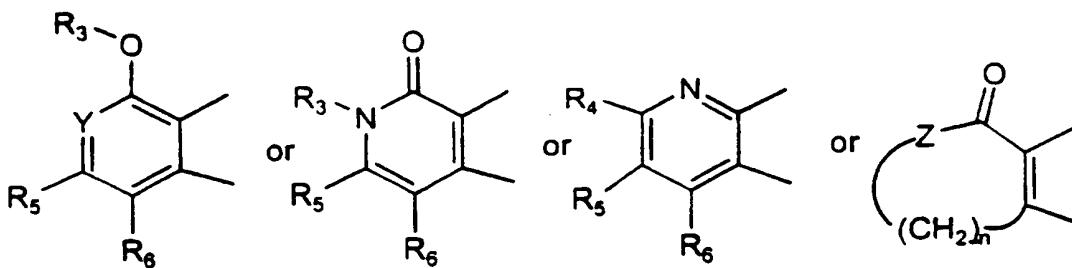
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3-7 carbon atoms; and



represents

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wherein:

Y represents nitrogen or C-R4;

Z represents N-R7 or a carbon atom substituted with R8 and R9, i.e., C(R8)(R9);

5

n is 1, 2, 3, or 4;

R3 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R4 is halogen or trifluoromethyl; or

-OR10, -COR10, -CO2R10, -OCOR10, or -R10, where R10 is hydrogen, phenyl,

10

2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

-CONR11R12 or -(CH2)mNR11R12, where m is 0, 1, or 2; R11 represents hydrogen, lower alkyl; and R12 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR11R12 forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

15

R5 and R6 are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy;

R7 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

20

R8 is hydrogen or lower alkyl; and

R9 is -COR13, -CO2R13 or -R13, where R13 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

25

R9 is -CONR14R15 or -(CH2)kNR14R15, where k is 0, 1, or 2; R14 represents hydrogen, lower alkyl; and R15 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is

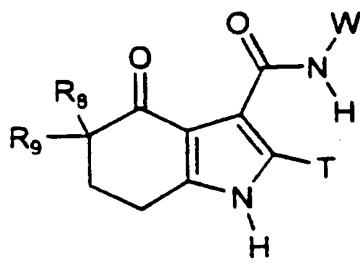
lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

These compounds are highly selective agonists, antagonists or inverse agonists for
5 GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa
brain receptors. In other words, while the compounds of the invention all interact with
GABAa brain receptors, they do not display identical physiologic activity. Thus, these
compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders,
overdose with benzodiazepine drugs and for enhancement of memory. For example, these
10 compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would
competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

In addition, the present invention encompasses compounds of Formula II.



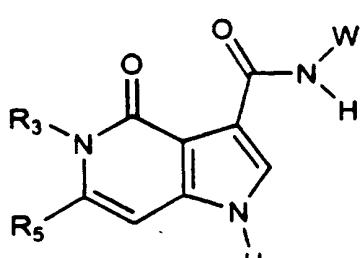
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II

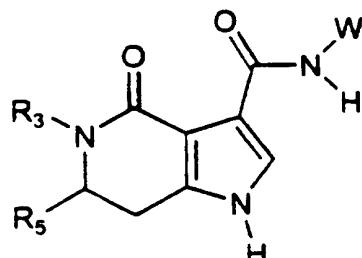
or the pharmaceutically acceptable non-toxic salts thereof wherein W, T, R8 and R9 are as defined above.

10

The present invention also encompasses compounds of Formula IIIa and IIIb:



IIIa



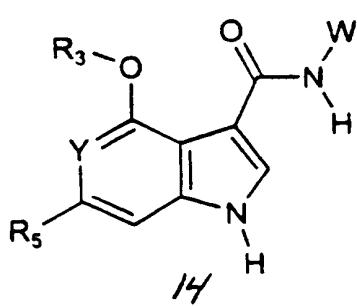
IIIb

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R3, and R5 are as defined above.

15

Preferred compounds of Formula IIIb are those where R3 is hydrogen or alkyl; and R5 is hydrogen.

The present invention also encompasses compounds of Formula IV:



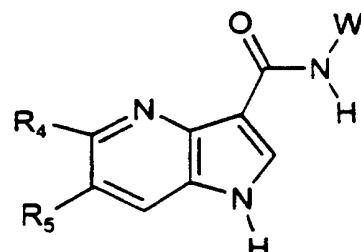
14

IV

or the pharmaceutically acceptable non-toxic salts thereof wherein W, Y, R₃, and R₅ are defined above.

5

The present invention also encompasses compounds of Formula V:

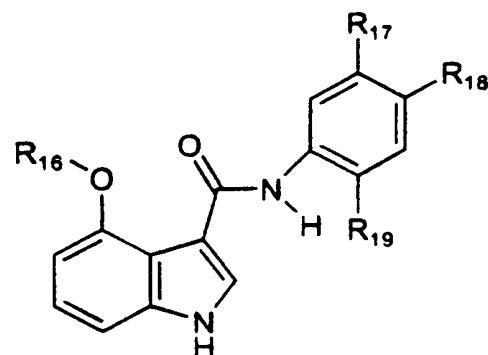


V

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R₄, and R₅ are defined above.

10

The invention further encompasses compounds of Formula VI:



VI

15

or the pharmaceutically acceptable non-toxic salts thereof wherein:

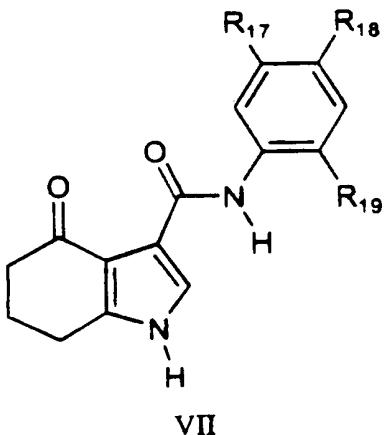
R₁₆ is hydrogen, benzyl or lower alkyl;

R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and R₁₉ is hydrogen, hydroxyl, or halogen.

5

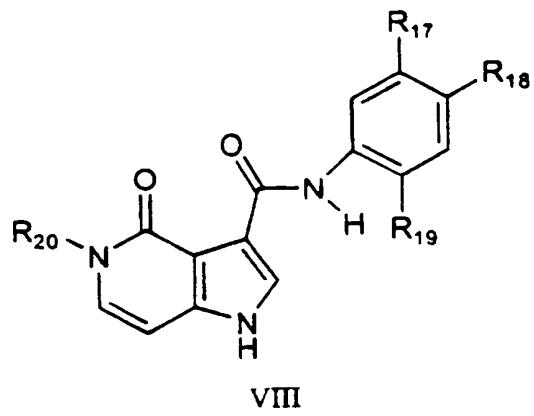
The invention additionally encompasses compounds of Formula VII:



10

or the pharmaceutically acceptable non-toxic salts thereof where R₁₇, R₁₈ and R₁₉ are defined above.

The invention further encompasses compounds of Formula VIII:

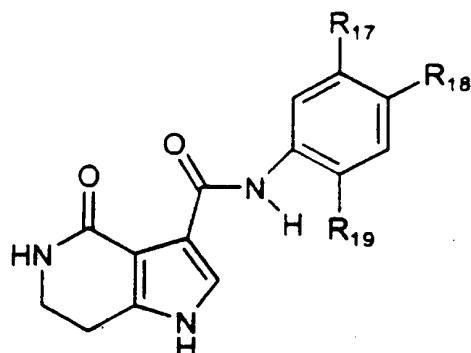


15

where R₁₇, R₁₈, and R₁₉ are defined above and R₂₀ is hydrogen or alkyl.

The invention further encompasses compounds of Formula IX:

16

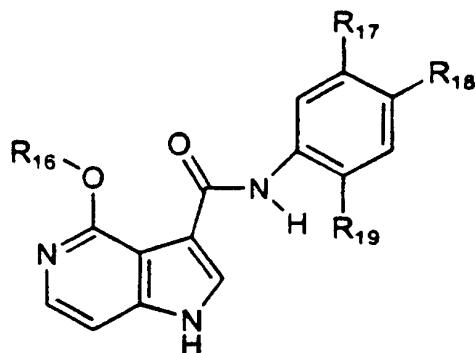


IX

where R₁₇, R₁₈, and R₁₉ are defined above.

5

The invention further encompasses compounds of Formula X:

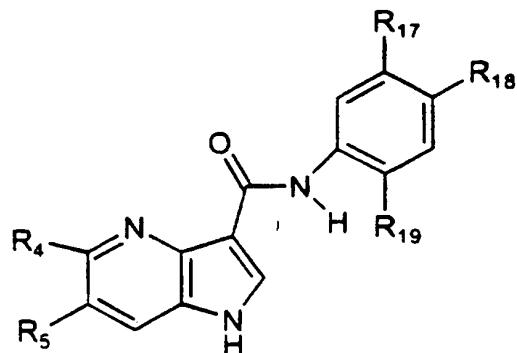


X

where R₁₆, R₁₇, R₁₈, and R₁₉ are defined above.

10

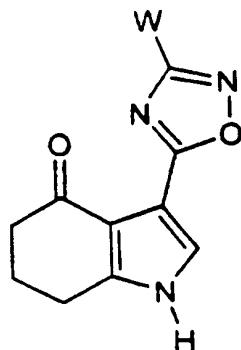
The invention further encompasses compounds of Formula XI:



XI

where R₄, R₅, R₁₇, R₁₈, and R₁₉ are defined above.

The invention further encompasses compounds of Formula XII:

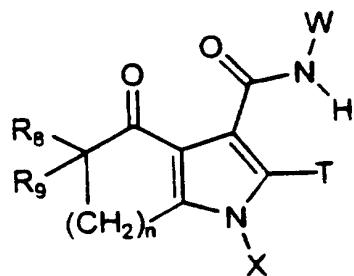


XII

5 wherein W represents phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen, cyano, hydroxy, lower alkyl, amino, mono or dialkylamino where each alkyl is independently lower alkyl, lower alkoxy, or NR₁COR₂, COR₂, CONR₁R₂ or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen or lower alkyl.

10

Further, the present invention provides compounds of Formula XIII:



XIII

wherein W, R₈ and R₉ are as defined above;

15 T represents hydrogen, amino, or nitro;

X is alkyl or hydrogen; and

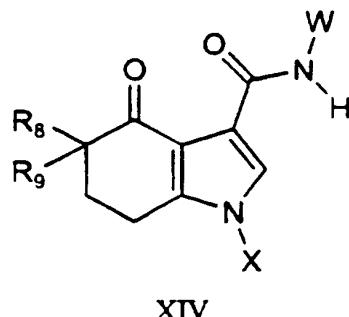
n is 1 or 2.

A preferred group of compounds of Formula XIII are those where R₈ and R₉ are independently alkyl or hydrogen; and n is 1. Another preferred group of compounds of Formula XIII are those where R₈ and R₉ are independently alkyl or hydrogen; and n is 2.

20

Particularly preferred compounds of Formula XIII where n is 2 are those where R₈ and R₉ are hydrogen; and X and T are both hydrogen.

The invention also provides compounds of Formula XIV:



5

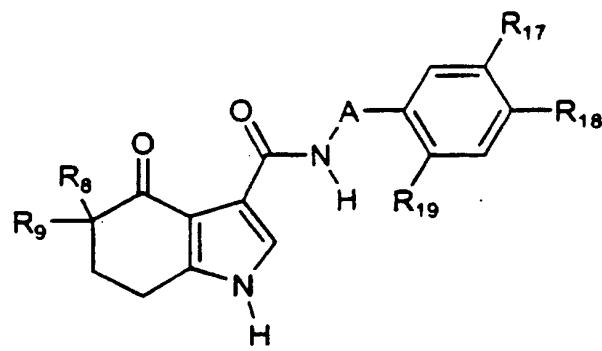
wherein W is as defined above;

R₈ and R₉ are independently alkyl or hydrogen; and

X is hydrogen, methyl, or ethyl.

10 Preferred compounds of Formula XIV are those where R₈ and R₉ are both hydrogen and X is hydrogen.

The present invention further provides compounds of Formula XV.



15

R₈ and R₉ are as defined above;

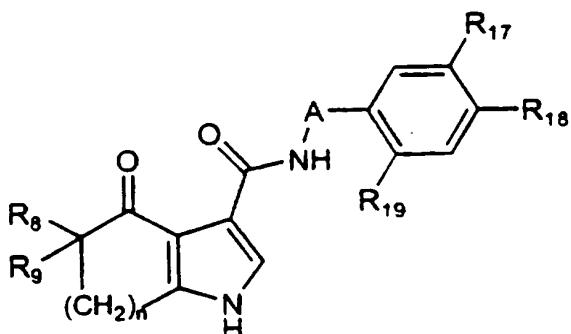
A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and R₁₉ is hydrogen, hydroxyl, or halogen.

5

The present invention also encompasses compounds of Formula XVI.



XVI

R₈ and R₉ are as defined above;

10 A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

n is 1 or 2;

15 R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

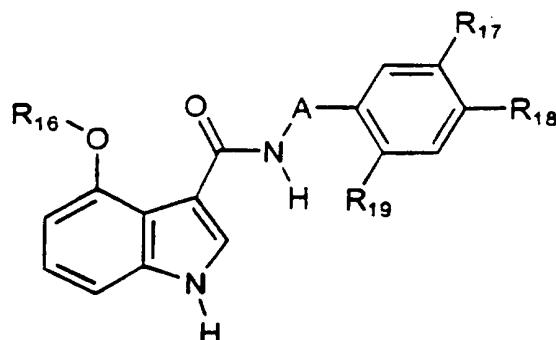
R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and

R₁₉ is hydrogen, hydroxyl, or halogen.

20

Further, the present invention provides compounds of Formula XVII.

20



XVII

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

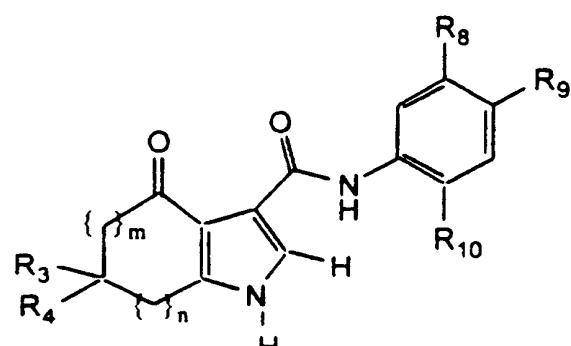
5 R₁₆ is hydrogen, benzyl, or lower alkyl;

R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

10 R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and

R₁₉ is hydrogen, hydroxyl, or halogen.

In addition, the present invention encompasses compounds of Formula DII.



DII

wherein

R₃ and R₄ are the same or different and represent hydrogen, alkyl, COR₅ or CO₂R₅ where

R₅ is alkyl or cycloalkyl having 3-7 carbon atoms, CONR₆R₇ where R₆ and R₇ are

20 selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms,

phenyl, 2-,3-, or 4-pyridyl, or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms;

R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, 5 amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

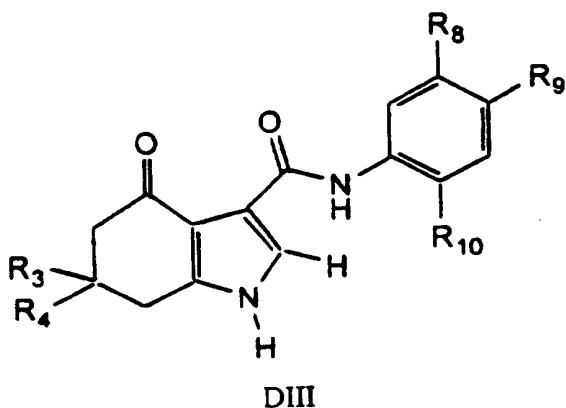
10 R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen.

15 In addition, the present invention encompasses compounds of Formula DIII.



wherein

20 R₃ and R₄ are the same or different and represent hydrogen or alkyl;

R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

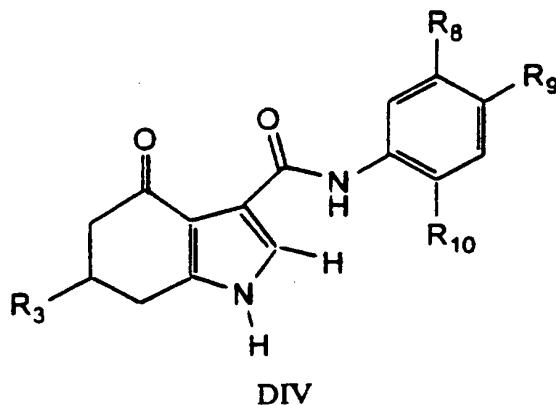
R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and

R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen. Particularly preferred compounds of Formula DIII are those where the phenyl group is trisubstituted in the 2,4, and 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen, and R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxyl, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DIV.



wherein

R₃ represents alkyl;

R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

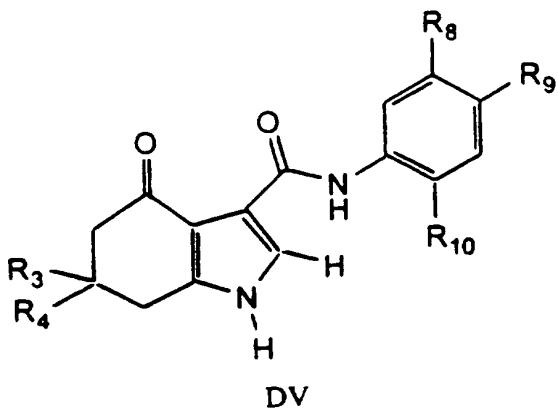
R₉ is hydrogen, halogen, cyano, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and

R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIV are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxyl, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DV.



wherein

R₃ and R₄ are the same or different and represent alkyl;

5 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

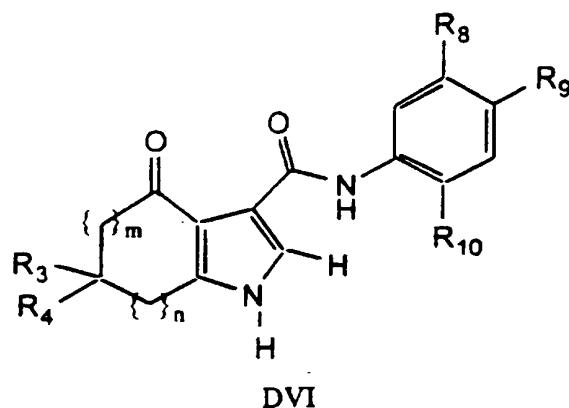
R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

10 R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DV are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen. Particularly preferred compounds of Formula DV are those where R₃ and R₄ are both methyl, and R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

20

In addition, the present invention encompasses compounds of Formula DVI



wherein

q is an integer of from 2-6;

5 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

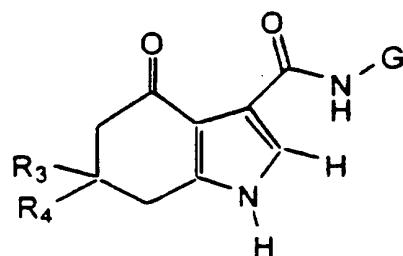
10 R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DVI are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DVII.



20

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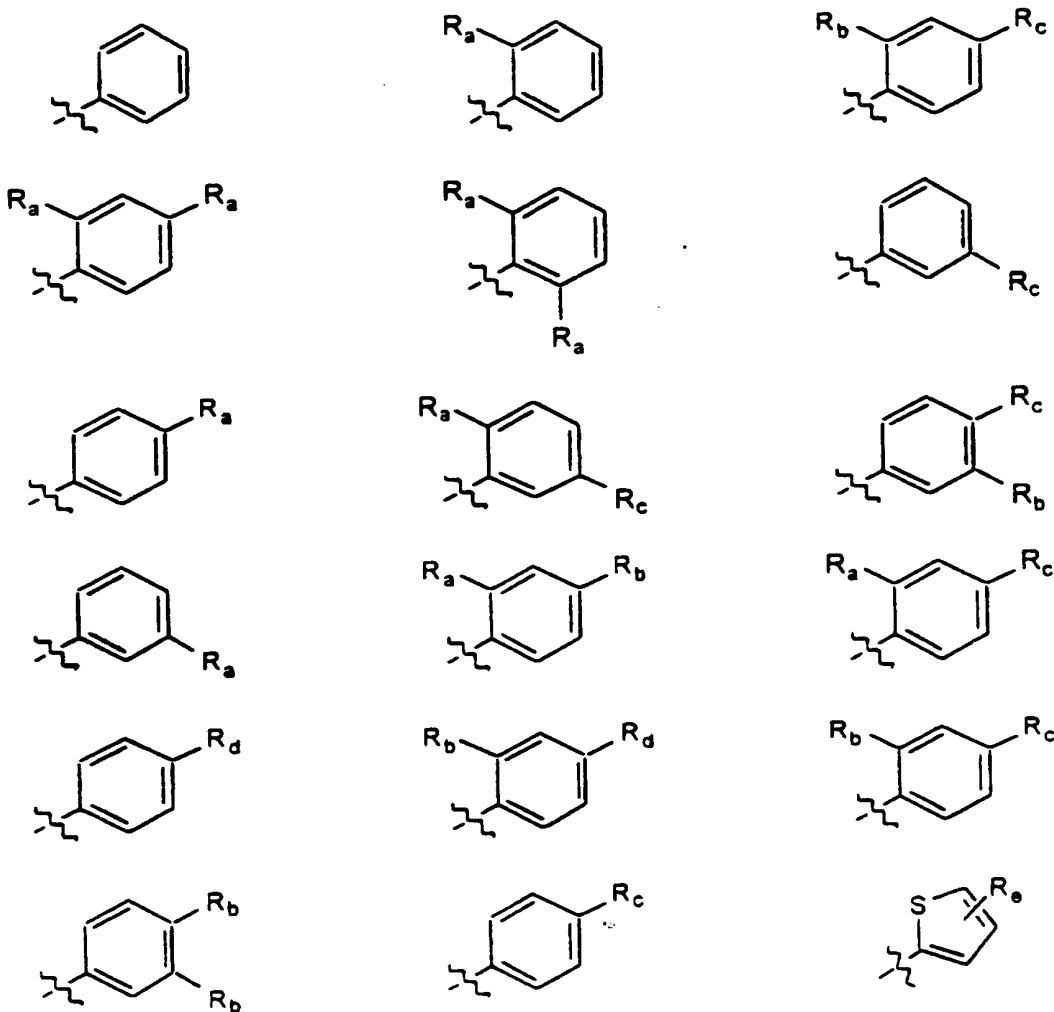
where

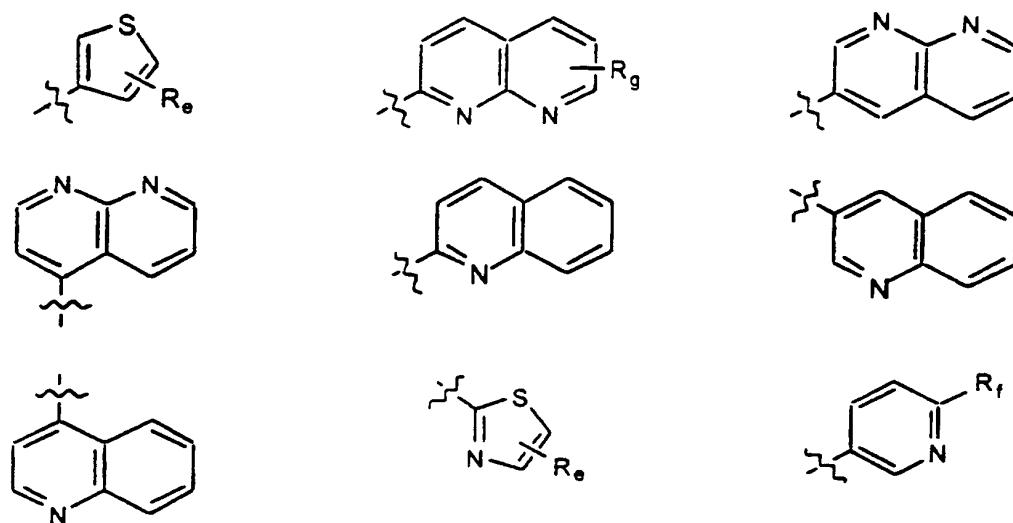
G represents aryl or heteroaryl such as, for example, thienyl, thiazolyl, pyridyl, naphthyridinyl, quinolinyl, or phenyl, each of which is optionally mono-, di- or trisubstituted with halogen alkyl alkoxy, or hydroxy; and

5 R₃ and R₄ are the same or different and represent hydrogen or alkyl, provided that not both R₃ and R₄ are hydrogen.

Preferred compounds of Formula DVII are those where R₃ and R₄ are C₁₋₃ alkyl, and more preferably methyl. Other preferred compounds of Formula DVII are those where R₃ is hydrogen and R₄ is C₁₋₃ alkyl, and more preferably R₄ is methyl.

10 Preferred compounds of Formula DVII include a G group selected from the following:





In the above G groups, the following definitions apply:

R_a is halogen;

R_b is hydroxy;

5 R_c represents alkoxy;

R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

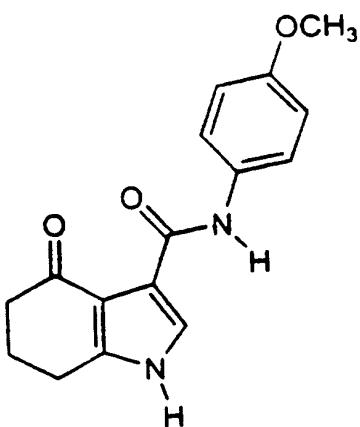
R_g represents hydrogen, R_a or R_c.

10 In those formulas where more than one of the same substituent appears, those substituents are the same or different.

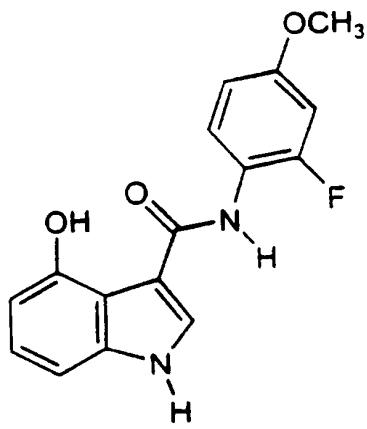
Particularly preferred R_a groups in G are fluorine. Particularly preferred R_c groups in G are methoxy and ethoxy. Particularly preferred R_d groups in G are methyl and ethyl.

15 Representative compounds of the invention are shown below in Table 1.

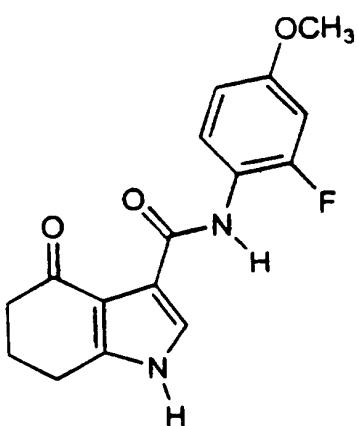
Table 1



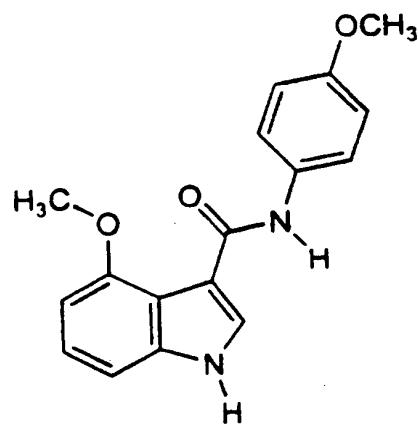
Compound 1



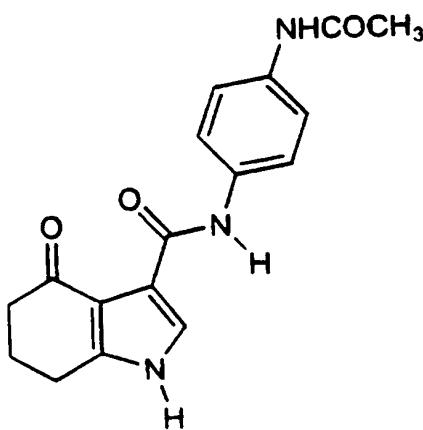
Compound 2



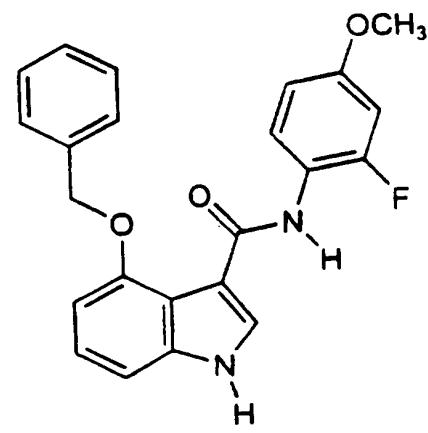
Compound 6



Compound 8

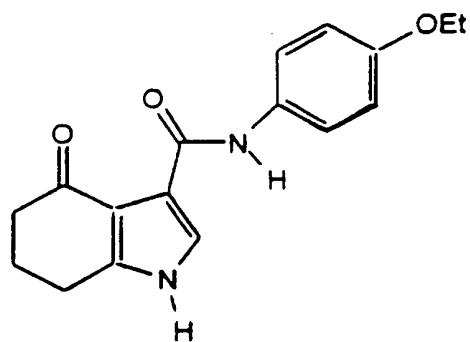


Compound 12

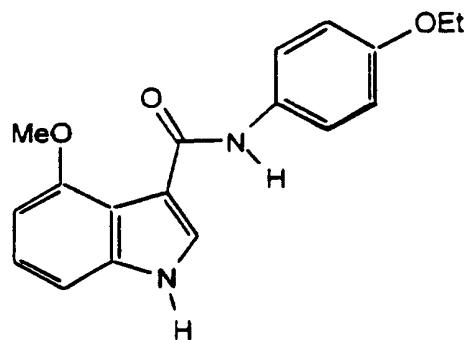


Compound 14

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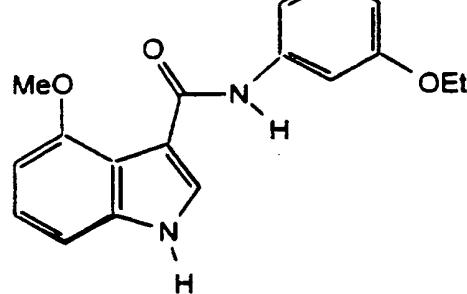


Compound 3

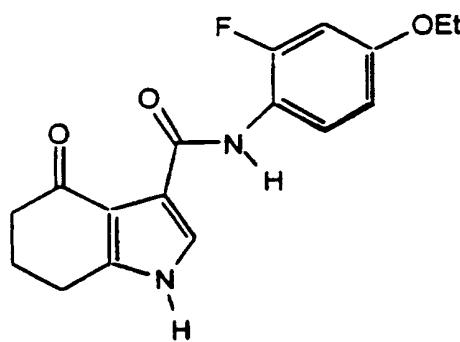


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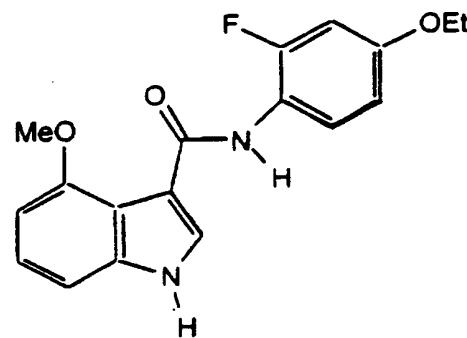
Compound 4



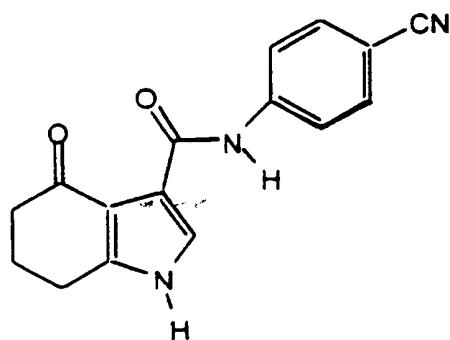
Compound 5



Compound 7

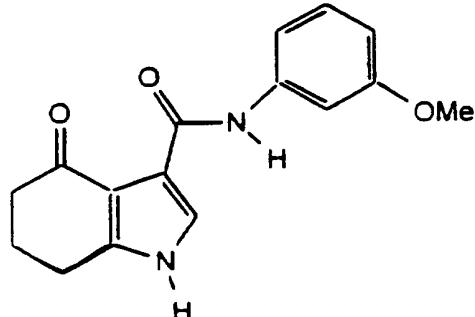


Compound 9



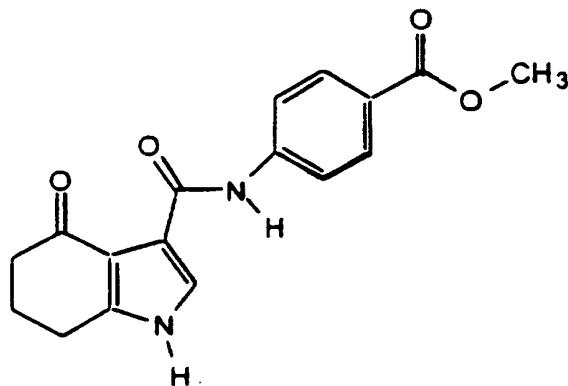
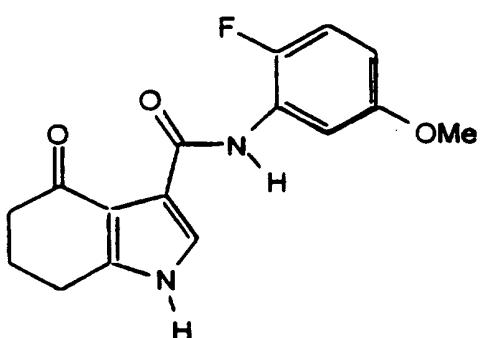
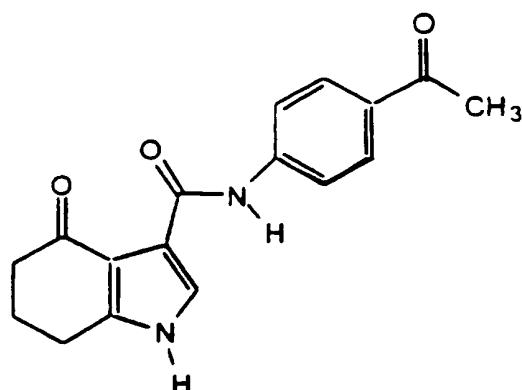
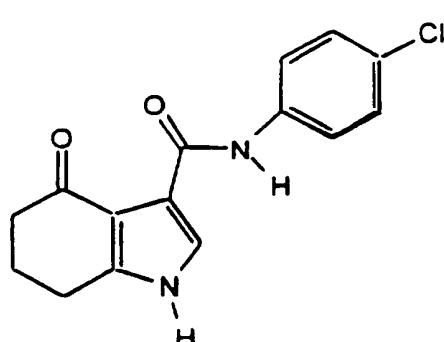
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Compound 10

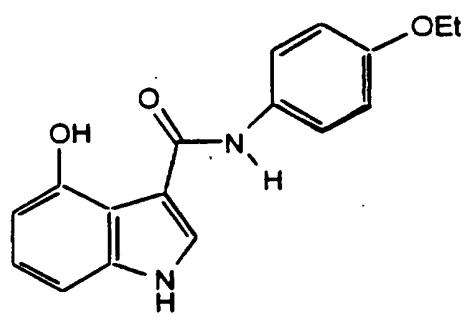
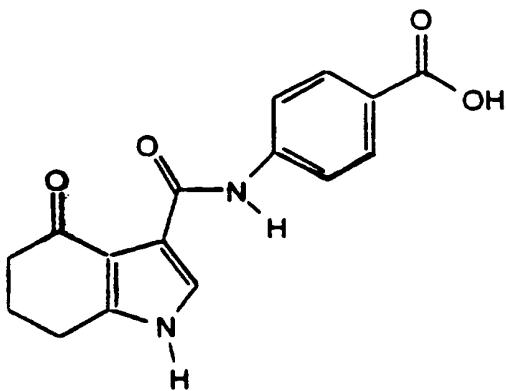


Compound 11

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5



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Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, ³⁰sulfuric, sulfenic, formic, toluenesulfonic,

methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH₂)_n-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the prodrugs, preferably acylated prodrugs, of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

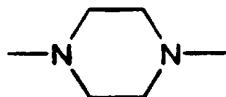
By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, 10 isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "phenylalkyl" as used herein is meant a phenyl group covalently bonded to an alkyl group as defined above and the alkyl group is covalently bonded to another moiety, such as, for example, a nitrogen atom.

15 By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxyl, neopentoxyl, hexoxy, 2-hexaoxy, 3-hexaoxy, and 3-methylpentoxyl.

20 By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "N-alkylpiperazyl" in the invention is meant radicals of the formula:



where R is a lower alkyl as defined above.

25 By "monoalkylamino" as used herein is meant an amino substituent substituted with one (1) alkyl group where the alkyl group is lower alkyl as defined above.

By "dialkylamino" as used herein is meant an amino substituent substituted with two (2) alkyl groups where the alkyl groups are independently lower alkyl groups as defined above.

30 By "alkylenedioxy" as used herein is meant a group of the formula -O-A-O- where A represents C₁-C₃ alkylene optimally substituted with up to two C₁-C₂ alkyl groups and each oxygen atom is covalently bound to the aromatic ring, i.e., the phenyl group. The oxygen

atoms of such alkylenedioxy groups are typically attached to adjacent carbon atoms of the aromatic ring.

The pharmaceutical utility of compounds of this invention are indicated by the following assay for GABAa receptor binding activity.

5 Assays are carried out as described in Thomas and Tallman (J. Bio. Chem. 156: 9838-9842, J. Neurosci. 3: 433-440, 1983). Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of 0.05 M Tris HCl buffer (pH 7.4 at 4°C). The tissue homogenate is centrifuged in the cold (4°) at 20,000 x g for 20'. The supernatant is decanted and the pellet is rehomogenized in the same volume of buffer and again centrifuged at 20,000 x g. The 10 supernatant is decanted and the pellet is frozen at -20°C overnight. The pellet is then thawed and rehomogenized in 25 volume (original wt/vol) of buffer and the procedure is carried out twice. The pellet is finally resuspended in 50 volumes (w/vol of 0.05 M Tris HCl buffer (pH 7.4 at 40°C).

15 Incubations contain 100 ml of tissue homogenate, 100 ml of radioligand 0.5 nM (³H-RO15-1788 [³H-Flumazenil] specific activity 80 Ci/mmol), drug or blocker and buffer to a total volume of 500 ml. Incubations are carried for 30 min at 4°C then are rapidly filtered through GF/B filters to separate free and bound ligand. Filters are washed twice with fresh 0.05 M Tris HCl buffer (pH 7.4 at 4°C) and counted in a liquid scintillation counter. 1.0 mM diazepam is added to some tubes to determine nonspecific binding. Data are collected in triplicate determinations, averaged and % inhibition of total specific binding is calculated. 20 Total Specific Binding = Total - Nonspecific. In some cases, the amounts of unlabeled drugs is varied and total displacement curves of binding are carried out. Data are converted to K_i values. Representative data for compounds of this invention are listed in Tables 2 and 3.

Table 2

<u>Compound Number</u>	<u>K_i(nM)</u>
1	4
2	430
6	1
8	25
12	28
14	133

Table 3

<u>Compound Number</u>	<u>K_i(nM)</u>
22	53
26	3
30	10
35	2
46	3
62	0.8
72	26
74	18
80	31
81	14
86	2
93	6
96	29
102	37

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic

pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional 5 excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring 10 phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, 15 propylene glycol, sorbitor or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may 20 also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or 25 suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures 30 but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended

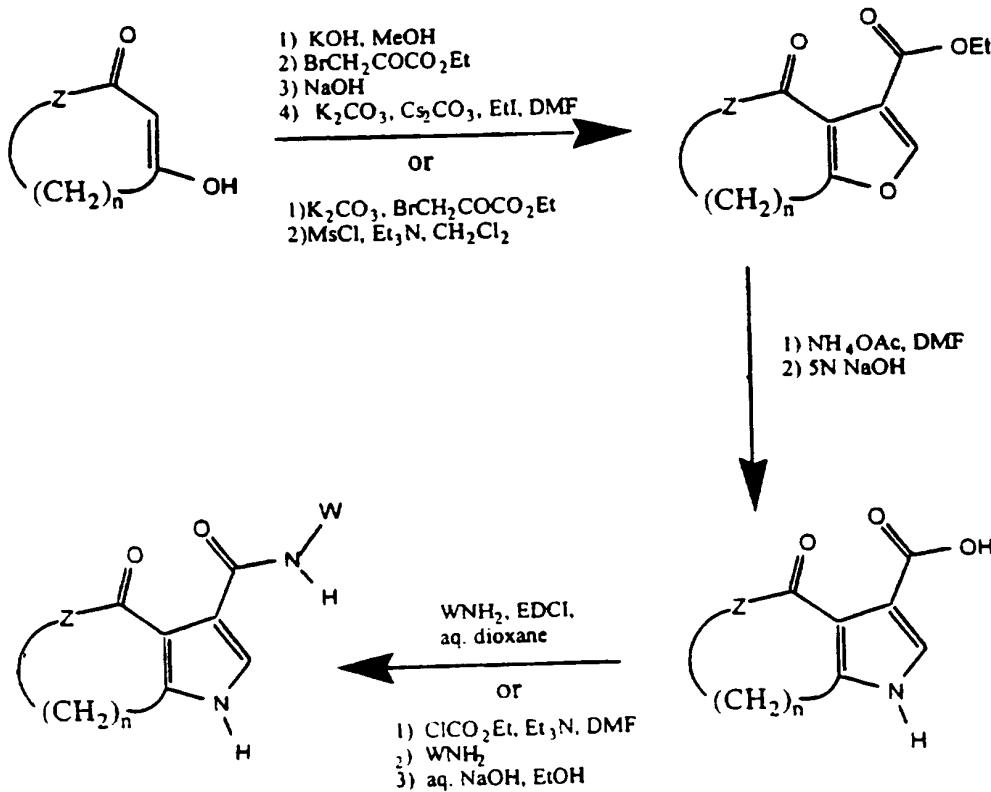
or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

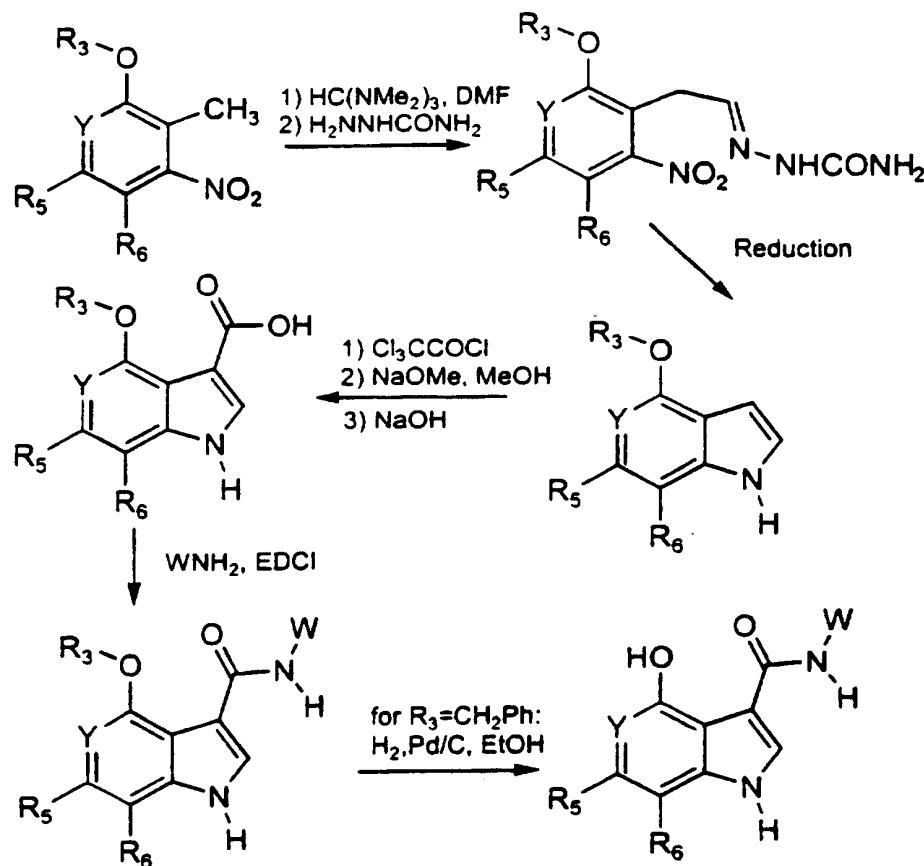
An illustration of the preparation of compounds of the present invention is given in Schemes I and II.

Scheme I



where W, Z, and n are as defined above.

Scheme II



W, R₃, Y, R₅, and R₆ are as defined above.

5 Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

10 The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

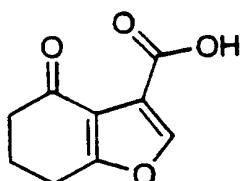
Example 1

Preparation of starting materials and intermediates

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known synthetic methods.

Representative examples of methods for preparing intermediates of the invention are set forth below.

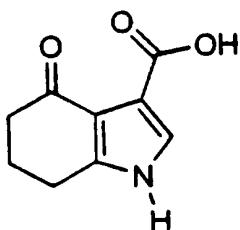
1. 4-Oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid



10 4-Oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid was prepared as follows: To a stirred solution of potassium hydroxide (28.06 g, 0.5 mol) in methyl alcohol (100 mL) under nitrogen at 0° C was added dropwise a solution of cyclohexanedione (56.07 g, 0.5 mol) in methyl alcohol (100 mL). The mixture was stirred at 0° C for 0.5 h, then a solution of ethyl bromopyruvate (66 mL, 0.525 mol) in methyl alcohol (100 mL) was added dropwise. After allowing the mixture to stir at ambient temperature for 17 h, a 50% aqueous sodium hydroxide solution (60 mL) was added dropwise and stirring continued an additional 7 h. After dilution with water, the solution was acidified and the methanol removed *in vacuo*. Ice water was added and the precipitate filtered and dried *in vacuo* to afford 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid. m.p. 137-138 °C.

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20 2. 4-Oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid

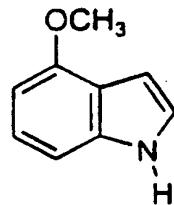


To a stirred suspension of 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid (28.2 g, 157 mmol) in ethyl alcohol (500 mL) under nitrogen at ambient temperature was added acetyl chloride (56 mL, 783 mmol) dropwise. After stirring 1 h, the solution was then heated

at reflux for 1 h. The solution was cooled and concentrated *in vacuo*. The residue was taken up into dichloromethane, washed with aqueous sodium bicarbonate, washed quickly with 1N sodium hydroxide, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford ethyl 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylate as an oil. A mixture of this ester (24.46 g, 117 mmol) and ammonium acetate (15.85 g, 206 mmol) in N,N-dimethylformamide (225 mL) was heated at 100°C under nitrogen for 1.25 h. The mixture was cooled, poured into ice water, and extracted two times with dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered, concentrated *in vacuo*, and the residue triturated with ether to give ethyl 4-oxo-4,5,6,7-tetrahydroindole-3-carboxylate. A mixture of this ester (11.31 g, 55 mmol) in 5N sodium hydroxide (200 mL) and ethanol (20 mL) was heated at reflux for 1 h. After cooling in an ice bath, the mixture was acidified with concentrated hydrochloric acid, the precipitate filtered, rinsed with ice water, and dried *in vacuo* to afford 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid. m.p. 269-270°C.

15 3. 4-Oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (m.p. 225-228 °C) is prepared essentially according to the procedure set forth in Example 1 and part 1 of this example.

20 4. 4-Methoxy-1H-indole

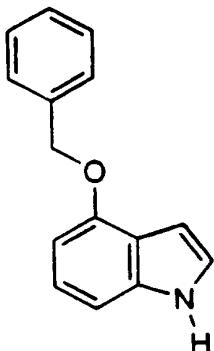


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A solution of 2-methyl-3-nitroanisole (9.96 g, 60 mmol) and tris(dimethylamino)methane (15.5 mL, 89 mmol) in dimethylformamide (30 mL) was heated at 115°C under nitrogen for 3 h. After cooling to ambient temperature a solution of semicarbazide hydrochloride (6.98 g, 63 mmol) and concentrated hydrochloric acid (5.3 mL) in water (75 mL) was added dropwise with vigorous stirring. The mixture was cooled further in an ice bath and the precipitate filtered, rinsed with ice water followed by, in sequence, cold 50% aqueous ethanol, cold ethanol, and ether, then dried to give a semicarbazone. The semicarbazone was suspended with 10% palladium on carbon (3 g) in ethanol (120 mL) in a Parr shaker and placed under a hydrogen atmosphere (50 psi) for 16 h. The mixture was

filtered through Celite and concentrated *in vacuo*. The residue was triturated with ice water, filtered and dried to give the title compound.

5. 4-Benzylxy-1H-indole

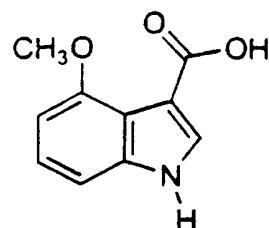


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A solution of 2-nitro-6-benzylxytoluene (13.0 g, 53 mmol) and tris(dimethylamino)methane (13.9 mL, 80 mmol) in dimethylformamide (30 mL) was heated at 115°C under Nitrogen for 3 h. Upon cooling to ambient temperature, a solution of semicarbazide hydrochloride (6.26 g, 56 mmol) and concentrated hydrochloric acid (4.8 mL) in water (70 mL) was added dropwise with vigorous stirring. Ethanol (25 mL) was added and the heterogeneous mixture stirred for 2 h. After cooling in an ice bath, the precipitate was filtered, rinsed with, in sequence, ice water, cold 50% aqueous ethanol, cold ethanol, then ether and dried to give a semicarbazone. A slurry of this semicarbazone (17.64 g, 54 mmol), Raney nickel (18 g of a 50% aqueous slurry) in 1:1 tetrahydrofuran:methanol (145 mL) was heated to 55°C. Hydrazine monohydrate was added in four equal portions (2.7 mL each) at 0.5 h intervals. The mixture was cooled, then filtered through a small pad of silica gel using ether. The filtrate was dried over magnesium sulfate, filtered, concentrated *in vacuo*, and the residue purified by flash chromatography to afford 4-benzylxy-1H-indole as a low melting solid.

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6a. 4-Methoxy-1H-indole-3-carboxylic acid



To a solution of 4-methoxy-1H-indole (7.15 g, 49 mmol) and pyridine (19.7 mL, 243 mmol) in dichloromethane (50 mL) at 0°C under nitrogen was added dropwise a solution of trichloroacetyl chloride (27.1 mL, 243 mmol) in dichloromethane (50 mL). After stirring at 5 0°C for an additional 1.5 h, the mixture was concentrated *in vacuo*. The residue was taken up in the minimal volume of methanol necessary and placed in a freezer overnight. The precipitate was filtered, rinsed well with methanol, and dried to yield 4-methoxy-3-trichloroacetyl-1H-indole. To a stirring solution of sodium methoxide (3.5 mL of a 25 weight % solution in methanol) in methanol (200 mL) at ambient temperature was added 4-methoxy-10 3-trichloroacetyl-1H-indole (9.07 g, 31.0 mmol) in portions over 0.75 h. After stirring an additional 0.75 h, the mixture was cooled in an ice bath, diluted with ice water, acidified with concentrated hydrochloric acid, and the methanol removed *in vacuo*. The resulting heterogeneous mixture was cooled in an ice bath, the precipitate filtered, rinsed with water, and dried to afford methyl 4-methoxy-1H-indole-3-carboxylic ester. A slurry of this ester 15 (5.6 g 27 mmol) in 50% aqueous sodium hydroxide (50 mL) and methanol (50 mL) was stirred at ambient temperature for 19 h. The mixture was cooled in an ice bath, acidified with concentrated hydrochloric acid, the precipitate filtered, rinsed with ice water, and dried to afford 4-methoxy-1H-indole-3-carboxylic acid.

20 **6b.** 4-Benzylxy-1H-indole-3-carboxylic acid was prepped in the same manner as 4-methoxy-1H-indole-3-carboxylic acid in 6a above.

7. 2-Cycloheptenone ethylene ketal

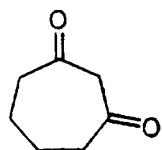


25 Bromine (44.8 g, 0.28 mol) was added dropwise to a stirred solution of cycloheptanone (28.5 g, 0.25 mol) in a 1:1 solution (300 mL) of ethylene glycol and

tetrahydrofuran at room temperature. The mixture was stirred for 5 hours, then poured into aqueous sodium bicarbonate and extracted 3X with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 2-bromocycloheptanone ethylene ketal(60 g). A mixture of this crude bromo ketal and a methanolic solution of sodium methoxide (250 mL, 25 wt. % solution) was heated at reflux overnight. The mixture was cooled to ambient temperature, poured into water, and extracted with hexanes. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-cycloheptenone ethylene ketal (39 g).

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8. 1,3-Cycloheptadione



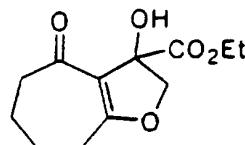
Mercury (II) acetate (80.7 g, 0.25 mol) was dissolved in water (150 mL), then tetrahydrofuran (150 mL) was added to give a suspension. To this stirring suspension was added 2-cycloheptenone ethylene ketal (39 g, 0.25 mol). After stirring at ambient temperature for 3 hours, the mixture was cooled in an ice water bath. A 10% aqueous sodium hydroxide solution (150 mL) was added, followed by a solution of sodium borohydride (4.8 g, 0.13 mol) in 10% aqueous sodium hydroxide (150 mL). The mixture was allowed to reach ambient temperature and stirred overnight. The mixture was saturated with sodium chloride, stirred for 30 minutes, then allowed to settle; the solution was decanted into brine and extracted with ethyl acetate, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 3-Hydroxycycloheptanone ethylene ketal (36 g).

To a solution of this crude hydroxy ketal and triethylamine (88.3 mL, 0.63 mol) in dichloromethane (250 mL) at 0° C was added, in one portion, sulfur trioxide pyridine complex (98.4 g, 0.63 mol) in methyl sulfoxide (250 mL). The mixture was allowed to ambient temperature, stirred for 1 hour, then cooled in an ice water bath. Brine was added, and the mixture extracted with diethyl ether. The organic layer was washed with aqueous 2N hydrochloric acid then brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1,3-cycloheptadione *mono* - ethylene ketal (32 g). A solution of this crude ketal in aqueous 2N hydrochloric acid (200 mL) and tetrahydrofuran (200 mL) was stirred at ambient temperature for 20 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate then

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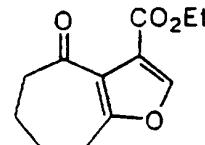
brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 1,3-cycloheptadione (16 g).

9. Ethyl 3-hydroxy-4-oxo-2,3,5,6,7,8-hexahydro-4H-cyclohepta[b]furan-3-carboxylate



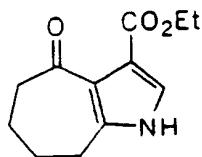
Ethyl bromopyruvate (26 g, 0.13 mol) was added dropwise to a stirred mixture of 1,3-cycloheptadione (16 g, 0.13 mol) and potassium carbonate (35 g, 0.25 mol) in dichloromethane (200 mL). After stirring overnight at ambient temperature, the solvent was removed *in vacuo*, diethyl ether was added and the mixture filtered through Celite. The filtrate was concentrated *in vacuo* to give the title compound (17 g).

10. Ethyl 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan-3-carboxylate



Methanesulfonyl chloride (9.7 g, 0.08 mol) was added dropwise to a stirring solution of ethyl 3-hydroxy-4-oxo-2,3,5,6,7,8-hexahydro-4H-cyclohepta[b]furan-3-carboxylate (17 g, 0.07 mol) and triethylamine (30 mL, 0.21 mol) in dichloromethane (100 mL) at 0° C. The mixture was allowed to reach ambient temperature, stirred for 2 hours, then poured into water and extracted with dichloromethane. The organic layer was washed sequentially with aqueous 2N sodium hydroxide, saturated aqueous sodium bicarbonate, and brine, then dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified on Silica gel (1:1 ethyl acetate / hexanes) to give the title compound.

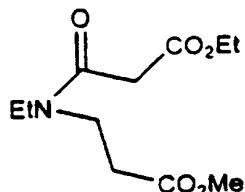
11. 4-Oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid



A mixture of ethyl 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan-3-carboxylate (3.48 g, 15.7 mmol) and ammonium acetate (2.41 g, 31.3 mmol) in N,N-dimethylformamide (25 mL) was heated at 115° C for 6 hours. The mixture was concentrated *in vacuo*, ice water was added, and extracted 2X with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate then brine, dried over sodium sulfate, filtered through a small pad of Silica gel (5% methyl alcohol / dichloromethane), and the filtrate concentrated *in vacuo* to give ethyl 4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylate (1.76 g). A solution of this ester in aqueous 5N sodium hydroxide (30 mL) and ethyl alcohol (6 mL) was heated at reflux for 1 hour, then cooled in an ice bath. The mixture was acidified with hydrochloric acid; the resulting precipitate was collected, rinsed with water followed by diethyl ether and allowed to dry to give 4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid (1.17 g). m.p. 225-227° C.

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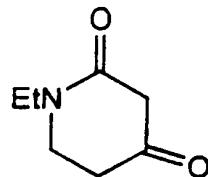
12. Ethyl N-ethyl, N-(3-methoxycarbonyl)propyl malonamide



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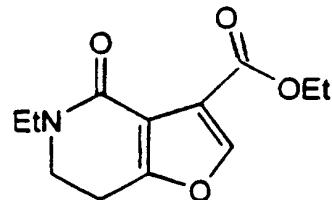
A solution of methyl acrylate (54 mL, 0.6 mol) in methyl alcohol (500 mL) was added dropwise to a stirred solution of ethylamine (340 mL, 6 mol) in methyl alcohol (1.5 L) at 0° C. After stirring an additional 45 minutes, the mixture was distilled *in vacuo* into one pot, then the solvent removed *in vacuo* (temperature <35° C). To the residue dissolved in dichloromethane (400 mL) at 0° C was added triethylamine (62.5 mL, 448 mmol) followed by a solution of ethyl malonyl chloride (54.4 mL, 427 mmol) in dichloromethane (100 mL). The mixture was stirred for 1 hour, then poured into saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate then water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (87.55 g).

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13. N-Ethyl-2,4-piperidione

A solution of ethyl N-ethyl, N-(3-methoxycarbonyl)propyl malonamide (87.55 g, 357 mmol) in methyl alcohol (350 mL) was added dropwise to a methanolic solution of sodium methoxide (25 wt.%, 163 mL) at ambient temperature. After heating at reflux for 1.5 hours, the reaction mixture was allowed to cool and concentrated *in vacuo*. After cooling the residue in an ice water bath, aqueous hydrochloric acid was added and extracted 2X with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give N-ethyl-3-methoxycarbonyl-2,4-piperidione (64.4 g). Some of this dione (57 g, 286 mmol) was heated at reflux in a mixture of hydrochloric acid (36 mL) and water (364 mL) for 3.5 hours. After cooling to ambient temperature, the solution was extracted 3X with ethyl acetate, the combined organic layer dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (9.54 g).

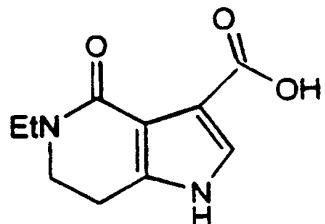
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14. Ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydro-furo[3,2-c]pyridine-3-carboxylate

To a stirred solution of potassium hydroxide (3.79 g, 67.6 mmol) in methyl alcohol (15 mL) under Nitrogen at 0°C was added dropwise a solution of N-ethyl-2,4-piperidione (9.54 g, 67.6 mmol) in methyl alcohol (20 mL). The mixture was stirred at 0°C for 1 hour, then a solution of ethyl bromopyruvate (8.9 mL, 71 mmol) in methyl alcohol (50 mL) was added dropwise. After allowing the mixture to stir at ambient temperature for 2.5 hours, a 50% aqueous sodium hydroxide solution (10 mL) was added dropwise and stirring continued 25 an additional 17 hours. After cooling in an ice water bath, the solution was acidified and the methanol removed *in vacuo*. Ice water was added and the precipitate filtered and dried *in*

vacuo to afford 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylic acid (3.91 g). More acid (1.15 g) was obtained via extraction of the aqueous filtrate 2X with ethyl acetate, drying over magnesium sulfate, filtration, concentrating *in vacuo*, and purification on Silica gel (5% methyl alcohol/dichloromethane). A stirring mixture of 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylic acid (4.94 g, 23.6 mmol), potassium carbonate (9.79 g, 70.8 mmol), cesium carbonate (770 mg, 2.4 mmol), and iodoethane (9.4 mL, 118 mmol) in N,N-dimethylformamide was heated at 85° C for 15.5 hours. The reaction mixture was cooled and concentrated *in vacuo*. Ethyl acetate was added, the mixture filtered, the filtrate washed with water, and the organic layer dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (4.5 g).

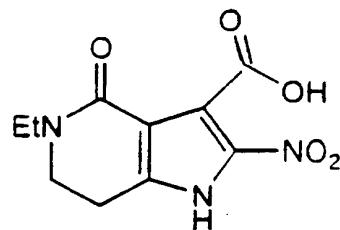
15. 4-Oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid



15. A mixture of ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylate (3.66 g, 15.4 mmol) and ammonium acetate (5.94 g, 77.1 mmol) in N,N-dimethylformamide (30 mL) was heated at 115° C for 23 hours. The mixture was cooled, concentrated *in vacuo*, ice water added, and the precipitate collected and dried to give ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylate (1.95 g). The aqueous filtrate was extracted 2X with ethyl acetate, the combined organic layers dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford additional ester (0.68 g). The combined materials were treated with aqueous 5N sodium hydroxide (75 mL) in dioxane (10 mL) at reflux for 2 hours. After cooling in an ice water bath, the mixture was acidified with aqueous hydrochloric acid, and concentrated *in vacuo*. Ethyl acetate was added, the mixture filtered, and the organic layer concentrated *in vacuo*. Trituration with ethyl acetate afforded 4-oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid (0.84 g).

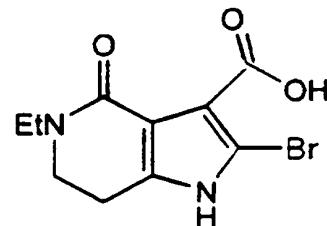
16. 2-Nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid

46



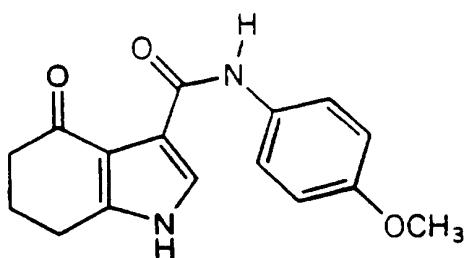
4-Oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol) was added in portions over 30 minutes to fuming nitric acid (2 mL) at 0° C. The mixture was stirred an additional 1.25 hours, then allowed to stir at ambient temperature for 1.25 hours. The mixture was poured into ice water and extracted 2X with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound(0.19 g).

17. 2-Bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid

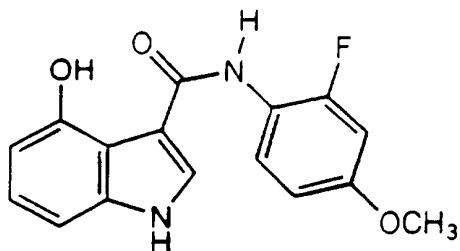


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To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (886 mg, 5 mmol) and catalytic benzoyl peroxide in N,N-dimethylformamide (5 mL) at 0° C was added N-bromosuccinimide (1.869 g, 10.5 mmol)in four equal portions over 1 hour. The mixture was stirred an additional hour, then poured into ice water, the precipitate collected and rinsed 15 with water then diethyl ether and dried. Purification on Silica gel (5% methyl alcohol in 1:1:1 dichloromethane/ ethyl acetate/ hexanes) gave 2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (376 mg).

Example 2**Compound 1**

A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol),
5 *p*-anisidine (616 mg, 5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride [EDCI] (959 mg, 5 mmol) in 50% aqueous 1,4-dioxane (10 mL) was stirred at
ambient temperature for 17 h. After concentrating *in vacuo*, the residue was taken up in 10%
methanol in ethyl acetate, washed with 1.3M hydrochloric acid then with aqueous sodium
bicarbonate, dried over magnesium sulfate, filtered, and concentrated *in vacuo*.
10 Recrystallization from ethyl acetate afforded N-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-
1H-indole-3-carboxamide (Compound 1); mp 219-220°C.

Example 3

(Compound 2)

5 N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (1.34 g, 3.4 mmol), prepared using the method above, was slurried with 10% palladium on carbon (134 mg) in ethanol (35 mL) in a Parr bottle and placed under a hydrogen atmosphere (50 psi) for 5 h. Methanol (5 ml) was added and the mixture returned to the Hydrogen atmosphere for an additional 18 h. The solution was filtered through Celite, concentrated *in vacuo*, and the residue purified by flash chromatography to afford N-(2-fluoro-4-methoxyphenyl)-4-hydroxy-
10 1H-indole-3-carboxamide (Compound 2) as a beige solid; mp 259-261°C (d).

Example 4

The following compounds were prepared essentially according to the procedures described in Examples 1-3:

15

(a) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 3); mp 217-218°C.

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(b) N-(4-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 4); mp 259-261°C (d).

(c) N-(3-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 5).

25

(d) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 6).

(e) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 7).

(f) N-(4-Methoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 8).

5 (g) N-(2-Fluoro-4-ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide
(Compound 9).

(h) N-(4-Cyanophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 10); mp 287-288°C.

10 (i) N-(3-Methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 11); mp 220-223°C.

15 (j) N-(4-Acetamidophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 12); mp 339-341°C.

(k) N-(4-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 13).

20 (l) N-(2-Fluoro-4-methoxyphenyl)-4-benzylxy-1H-indole-3-carboxamide
(Compound 14).

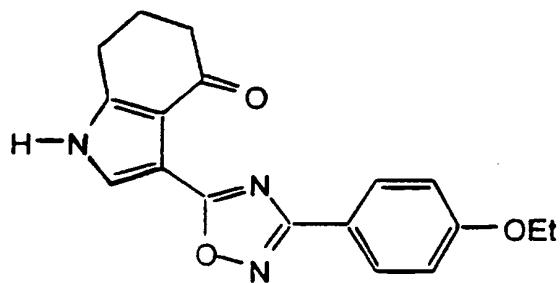
(m) N-(4-Acetylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 15).

25 (n) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 16).

(o) N-(4-Carbomethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 17); mp 261-262°C.

30 (p) N-(4-Carboxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 18).

- (q) N-(4-Ethoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 19).
- (r) N-(3-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 20).
- 5
(s) N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 21).
- 10 (t) N-(4-Isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 22).
- (u) N-(4-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 23).
- 15 (v) N-(4-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 24).
- (w) N-(4-Aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 25).
- 20 (x) N-(3-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 26); mp: 230-232°C.



- 25 (y) (compound 27)
- (z) N-(2-Fluoro-4-isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 28).

(aa) N-(4-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 29).

5 (ab) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 30); mp 193-194°C.

10 (ac) N-(4-Ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 31).

15 (ad) N-(4-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 32).

20 (ae) N-(2-Methoxy-5-bromophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 33).

(af) N-(3,4-Dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 34).

25 (ag) N-Phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35)
(Also, see Example 5).

(ah) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 36).

30 (ai) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 37), mp 213-215°C.

(aj) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 38).

(ak) N-(4-Ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 39).

5 (al) N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 40).

(am) N-(3-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 41).

10 (an) N-(2-Amino-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 42).

(ao) N-(4-Methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 43).

15 (ap) N-Phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 44).

20 (aq) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 45).

(ar) N-(2-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 46).

25 (as) N-(3-Fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 47).

(at) N-(2-(4-Hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 48).

30 (au) N-(2-(4-Ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 49).

(av) N-(4-Ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 50) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-ethoxyphenyl)formamide).

5 (aw) N-(2-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 51) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluorophenyl)formamide).

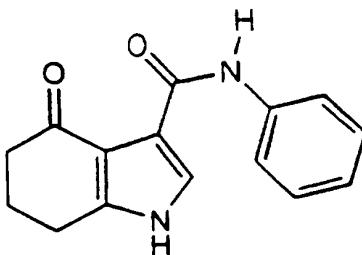
10 (ax) N-Phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 52) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-phenylformamide).

15 (ay) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 53) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-methoxyphenyl)formamide).

20 (az) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 54) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-ethoxyphenyl)formamide).

25 (ba) N-(4-Fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 55).

Example 5

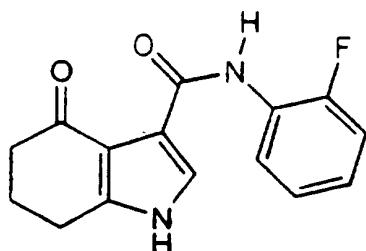


Compound 35

A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol), aniline (0.46 mL, 5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
54

hydrochloride (959 mg, 5 mmol) in 50% aqueous dioxane (10 mL) was allowed to stir at ambient temperature for 17.5 hours, then concentrated *in vacuo*. The residue was cooled in an ice water bath, aqueous 3.6 N hydrochloric acid was added, and the precipitate collected, rinsed with aqueous 3.6 N hydrochloric acid then water and dried. Recrystallization from 5 ethyl alcohol afforded N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35) (164 mg). mp 225-226° C.

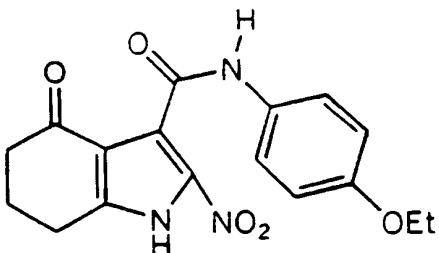
Example 6



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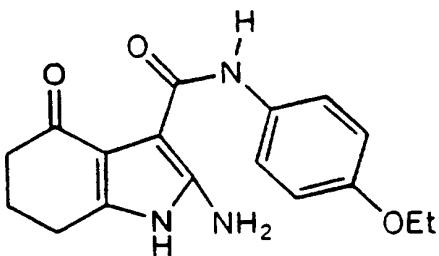
Compound 46

To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (538 mg, 3 mmol) and triethylamine (0.88 mL, 6.3 mmol) in N,N-dimethylformamide (15 mL) at 0° C was added ethyl chloroformate (0.57 mL, 6 mmol). After stirring at 0° C for 45 minutes, 2-fluoroaniline (0.58 mL, 6 mmol) was added. The mixture was stirred for an additional 45 15 minutes, then allowed to stir at ambient temperature for 14 hours. The mixture was poured into aqueous 1.2 N hydrochloric acid and extracted 2X with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. To the residue was added aqueous 1N sodium hydroxide (10 mL) and ethyl alcohol (2 mL) and the mixture heated at reflux for 4.5 hours. After cooling in an ice 20 water bath, the mixture was acidified with aqueous hydrochloric acid, the precipitate collected, rinsed with water and dried. Recrystallization from ethyl alcohol afforded N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46) (530 mg). mp 238-240° C.

Example 7

(Compound 56)

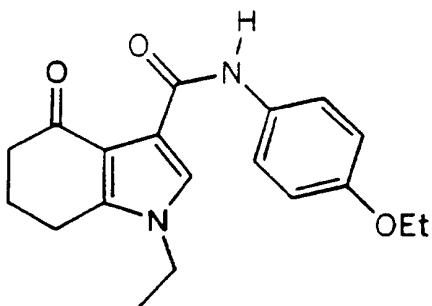
A mixture of 2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (0.18 g, 0.8 mmol), *p*-phenetidine (0.52 mL, 4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (767 mg, 4 mmol) in 50% aqueous dioxane (10 mL) was stirred for 67 hours, then concentrated *in vacuo*. Aqueous 3.6 N hydrochloric acid was added, the mixture cooled in an ice water bath, and the precipitate collected, rinsed with water then diethyl ether, and dried. Purification on Silica gel (10% methyl alcohol/dichloromethane) gave N-(4-ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 56) (51 mg).

Example 8

(Compound 57)

N-(4-Ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (41 mg) was treated with 10% palladium on carbon (5 mg) in ethyl alcohol (10 mL) under hydrogen (50 PSI) in a Parr bottle for 1 hour. The mixture was filtered through Celite, concentrated *in vacuo*, and purified on Silica gel (5% methyl alcohol/dichloromethane) to afford N-(4-ethoxyphenyl)-2-amino-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 57) (12 mg).

56

Example 9

(Compound 58)

A mixture of N-(4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (204 mg, 0.7 mmol), potassium carbonate (188 mg, 1.4 mmol), cesium carbonate (22 mg, 0.1 mmol), and iodoethane (0.08 mL, 1 mmol) in N,N-dimethylformamide was heated at 85° C for 1 hour. The mixture was cooled and filtered using ethyl acetate. The solid was set aside; the organic layer was washed with water, dried over magnesium sulfate, filtered, concentrated *in vacuo*, and triturated with diethyl ether to give N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (73 mg). The set-aside solid was slurried in aqueous hydrochloric acid, the precipitate collected, rinsed with water and dried to give additional amide (Compound 58) (94 mg). mp. 209-210° C.

Example 10

The following compounds are prepared essentially according to the procedures described in Examples 1-9:

(a) N-(3-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 59); mp 235-237° C.

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(b) N-(4-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 60); mp 259-261° C.

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(c) N-(2-Hydroxy-4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

carboxamide (Compound 61); mp 252-254° C.

(d) N-(2-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 62); mp 215-216°C.

(e) N-(4-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

5 (Compound 63); mp 313-315°C.

(f) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

carboxamide (Compound 64); mp 335-338°C (d).

10 (g) N-(3,4-Dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 65).

(h) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

carboxamide (Compound 66 mp 328-331°C (d).

15

(i) N-(3-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 67); mp 227-228°C.

(j) N-(2-Fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

20 carboxamide (Compound 68); mp 216-217°C.

(k) N-(3-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 69).

25

(l) N-(2-Fluoro-5-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

carboxamide (Compound 70); mp 223-225°C.

(m) N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide

(Compound 71); mp 220-222°C.

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(n) N-(2-Fluoro-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-

carboxamide (Compound 72); mp 181-183°C.

(o) N-(2-Hydroxy-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 73); mp 238-240° C.

5 (p) N-[4-(Methylamino)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 74); mp 242-244° C.

10 (q) N-(4-Aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 75); mp 207-210° C.

(r) N-(3-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 76).

15 (s) N-(2-Hydroxy-4-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 77); mp 190-195° C.

(t) N-(4-Ethoxyphenyl)-2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 78).

20 (u) N-(4-Ethoxyphenyl)-2-chloro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 79).

(v) N-Phenyl-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 80); mp 248-251 ° C.

25 (w) N-(2-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 81); mp 214-216° C.

(x) N-(3-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 82); mp 247-249° C.

(y) N-(4-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 83). *59*

(z) N-(3-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 84).

5 (aa) N-(3-Methylphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 85); mp 233-234° C.

(ab) N-(4-Hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 86); mp 301-303° C.

10 (ac) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 87); mp 340° C.

15 (ad) N-(4-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 88).

(ae) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 89).

20 (af) N-(4-Ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 90).

(ag) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 91); mp 178-180° C.

25 (ah) N-Phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 92); mp 218-219° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-phenylformamide).

30 (ai) N-(2-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 93) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluorophenyl)formamide).

(aj) N-(3-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 94) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(3-fluorophenyl)formamide).

5

(ak) N-(4-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 95) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-fluorophenyl)formamide).

10

(al) N-(3-Methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 96); mp 190 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(3-methoxyphenyl)formamide).

15

(am) N-(4-Hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 97); mp 278-280 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-hydroxyphenyl)formamide).

20

(an) N-(4-Methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 98); mp 178-179 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-methoxyphenyl)formamide).

25

(ao) N-(4-Ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 99); mp 198-201 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-ethoxyphenyl)formamide).

30

(ap) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 100); mp 158-159 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-methoxyphenyl)formamide).

(aq) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 101); mp 305-308° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-hydroxyphenyl)formamide).

5

(ar) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 102); mp 172-174° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-ethoxyphenyl)formamide).

10

(as) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 103) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-5-methoxyphenyl)formamide).

15

(at) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 104); mp 150-152 °C.

20

(au) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 105); mp 145-147° C.

(av) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 106); mp 154-155° C.

25

(aw) N-(4-Ethoxyphenyl)-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 107); mp 215-216° C.

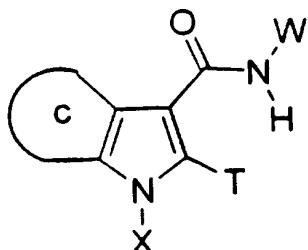
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The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims.

To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

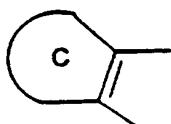
WHAT IS CLAIMED IS:

1. A compound of the formula:

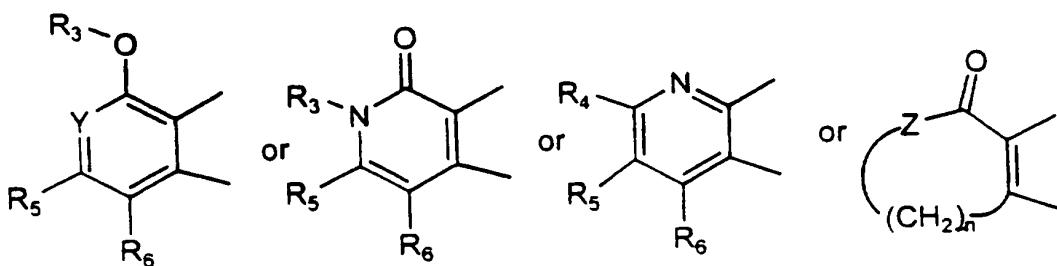


or the pharmaceutically acceptable non-toxic salts thereof wherein:

- 5 T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;
- X is hydrogen, hydroxyl or lower alkyl;
- 10 W is phenyl or phenylalkyl where each alkyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and



15 represents



wherein:

Y represents nitrogen or C-R4;

represents N-R7 or a carbon atom substituted with R8 and R9;

n is 1, 2, 3, or 4;

64

R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R₄ is halogen or trifluoromethyl; or

-OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 5
2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

-CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents 10
hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

10

R₅ and R₆ are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy;

15

R₇ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R₈ is hydrogen or lower alkyl; and

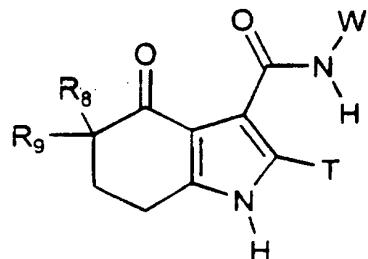
R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

20

R₉ is -CONR₁₄R₁₅ or -(CH₂)_kNR₁₄R₁₅, where k is 0, 1, or 2; R₁₄ represents hydrogen, lower alkyl; and R₁₅ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

25

2. A compound of the formula:



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or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

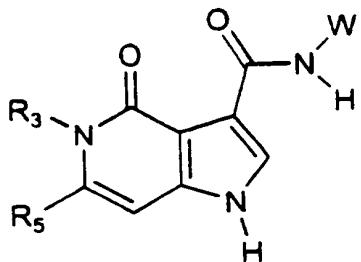
T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;

R₈ is hydrogen or lower alkyl; and

R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

R₉ is -CONR₁₄R₁₅ or -(CH₂)_kNR₁₄R₁₅, where k is 0, 1, or 2; R₁₄ represents hydrogen, lower alkyl; and R₁₅ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

3. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

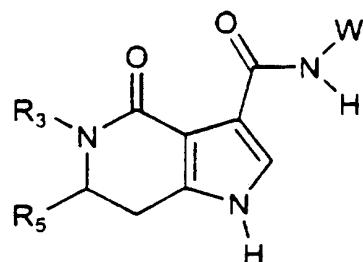
W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

5

4. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneoxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

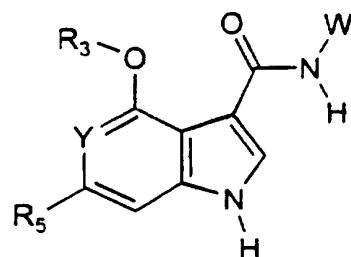
10

R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

15

5. A compound of the formula:



20

or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7

or

carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

5 R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

Y is nitrogen or C-R₄;

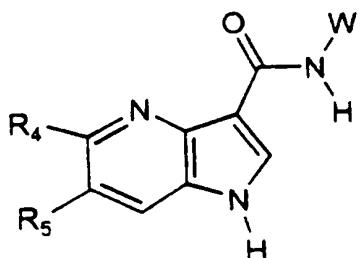
R₄ is halogen or trifluoromethyl; or

10 R₄ is -OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

15 R₄ is -CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

20 6. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₄ is halogen or trifluoromethyl; or

R₄ is -OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

5 R₄ is -CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl 10 piperazinyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

7. A compound according to claim 1, which is N-(3-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

8. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide.

20 9. A compound according to claim 1, which is N-(4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

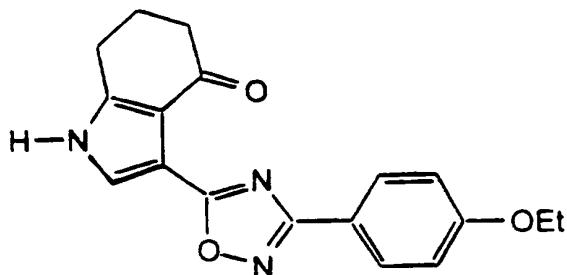
25 11. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 12. A compound according to claim 1, which is N-(4-aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

13. A compound according to claim 1, which is N-(3-fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

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14. A compound according to claim 1, which is



5 15. A compound according to claim 1, which is N-(2-fluoro-4-isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

16. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 17. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 18. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

19. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 20. A compound according to claim 1, which is N-(2-methoxy-5-bromophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

21. A compound according to claim 1, which is N-(3,4-dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 22. A compound according to claim 1, which is N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

23. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

24. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 26. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

27. A compound according to claim 1, which is N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 28. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

29. A compound according to claim 1, which is N-(2-amino-4-methylphenyl)-4-oxo-20 4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30. A compound according to claim 1, which is N-(4-methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 31. A compound according to claim 1, which is N-phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

32. A compound according to claim 1, which is N-(3-hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 45)

30 33. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

34. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 35. A compound according to claim 1, which is N-(2-(4-hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

36. A compound according to claim 1, which is N-(2-(4-ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 37. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

38. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

15 39. A compound according to claim 1, which is N-phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

20 40. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

41. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

25 42. A compound according to claim 1, which is N-(4-fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

43. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 44. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

45. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-amino-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 46. A compound according to claim 1, which is N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

47. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 48. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

49. A compound according to claim 1, which is N-(2-hydroxy-4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 50. A compound according to claim 1, which is N-(2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 51. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

52. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 53. A compound according to claim 1, which is N-(3,4-dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

54. A compound according to claim 1, which is N-(3-hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 55. A compound according to claim 1, which is N-(3-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

56. A compound according to claim 1, which is N-(2-fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

57. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

58. A compound according to claim 1, which is N-(2-fluoro-5-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 59. A compound according to claim 1, which is N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

60. A compound according to claim 1, which is N-(2-fluoro-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 61. A compound according to claim 1, which is N-(2-hydroxy-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 62. A compound according to claim 1, which is N-[4-(methylamino)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

63. A compound according to claim 1, which is N-(4-aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 64. A compound according to claim 1, which is N-(3-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

65. A compound according to claim 1, which is N-(2-hydroxy-4-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 66. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

67. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-chloro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 68. A compound according to claim 1, which is N-phenyl-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

69. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 70. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

71. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 72. A compound according to claim 1, which is N-(3-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 73. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

74. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 75. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

76. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 77. A compound according to claim 1, which is N-(2-fluoro-5-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

78. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 79. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

80. A compound according to claim 1, which is N-phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

10 81. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

82. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

15 83. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

20 84. A compound according to claim 1, which is N-(3-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

85. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

25 86. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

87. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

30 88. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

89. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

90. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

91. A compound according to claim 1, which is N-(2-fluoro-5-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

92. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

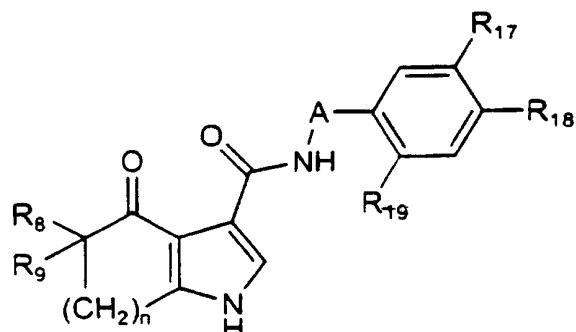
93. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

94. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

95. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

96. A compound according to claim 1, which is N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

97. A compound of the formula:



wherein:

R₈ and R₉ are independently alkyl or hydrogen;

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

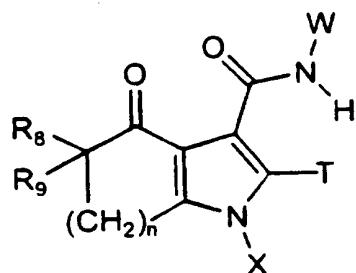
n is 1 or 2;

5 R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and

10 R₁₉ is hydrogen, hydroxyl, or halogen.

98. A compound of the formula:



15 wherein

W is phenyl or phenylalkyl where each alkyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₈ is hydrogen or lower alkyl; and

25 R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

T represents hydrogen, amino, or nitro;

X is alkyl or hydrogen; and

n is 1 or 2.

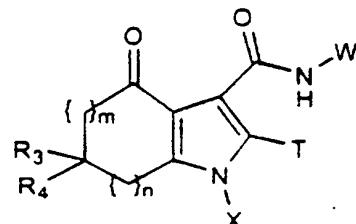
- 5 99. A compound according to claim 98, wherein
 R₈ and R₉ are independently alkyl or hydrogen;
 X and T are hydrogen;
 W is phenyl optionally substituted with up to two groups selected from halogen, hydroxy,
 lower alkyl, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or
 10 cycloalkyl having 3-7 carbon atoms, and lower alkoxy;
 and n is 2.

100. A compound according to claim 99, wherein W is phenyl mono- or
 disubstituted with a substituent selected from halogen and alkoxy.

15

101. A compound according to claim 97, wherein n is 2.

102. A compound of the formula:



- 20 or the pharmaceutically acceptable non-toxic salts thereof wherein:
 W is aryl or heteroaryl, each of which is optionally substituted with up to five groups selected
 independently from
 halogen, cyano, hydroxy, alkyl or cycloalkyl having 3-7 carbon atoms,
 amino or mono- or dialkylamino where each alkyl is independently lower alkyl or
 25 cycloalkyl having 3-7 carbon atoms,
 alkoxy or cycloalkyl alkoxy having 3-7 carbon atoms, or
 NR₁COR₂, COR₂, CONR₁R₂ or CO₂R₂ where R₁ and R₂ are the same or different
 and represent hydrogen or alkyl or cycloalkyl having 3-7 carbon atoms; and
 T is halogen, hydrogen, hydroxyl, amino or alkoxy;

X is hydrogen, hydroxyl or alkyl;

m is 0, 1, or 2;

n is 0, 1, or 2; and

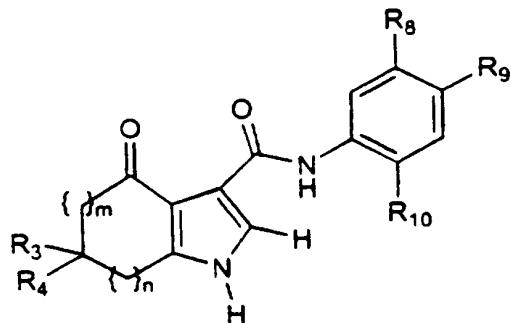
R₃ and R₄ are the same or different and represent hydrogen, alkyl, COR₅ or CO₂R₅ where

5 R₅ is alkyl or cycloalkyl having 3-7 carbon atoms, CONR₆R₇ where R₆ and R₇ are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms, phenyl, 2-,3-, or 4-pyridyl, or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms.

10

103. A compound of the formula:



wherein

R₃ and R₄ are the same or different and represent hydrogen, alkyl, COR₅ or CO₂R₅ where

15 R₅ is alkyl or cycloalkyl having 3-7 carbon atoms, CONR₆R₇ where R₆ and R₇ are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms, phenyl, 2-,3-, or 4-pyridyl, or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms;

20 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

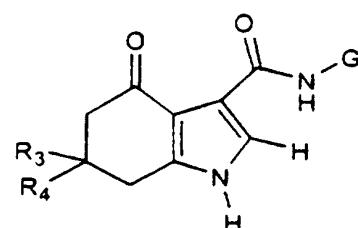
R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

5

104. A compound of the formula:

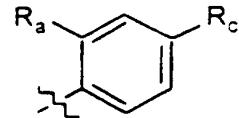
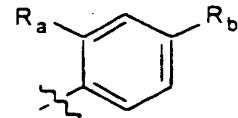
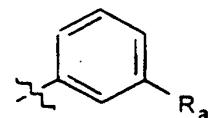
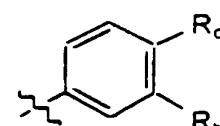
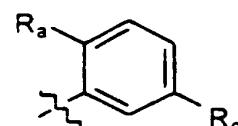
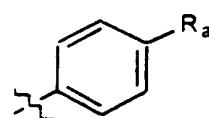
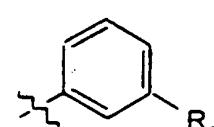
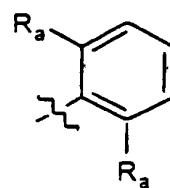
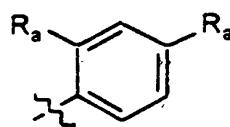
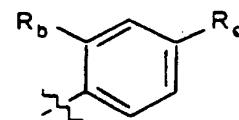
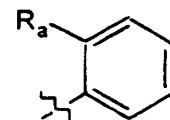
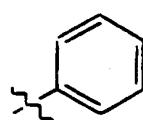


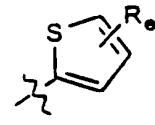
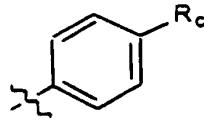
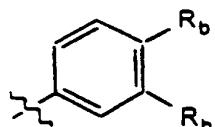
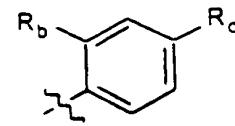
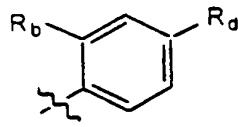
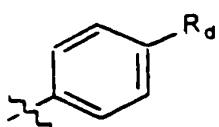
where

G represents thieryl, thiazolyl, pyridyl, naphthyridinyl, quinolinyl, or phenyl, each of which is optionally mono-, di- or trisubstituted with halogen, alkyl, alkoxy, or hydroxy; and

10 R₃ and R₄ are the same or different and represent hydrogen or alkyl, provided that not both R₃ and R₄ are hydrogen.

105. A compound according to claim 104, wherein G is selected from the following:





wherein, independently,

R_a is halogen;

R_b is hydroxy;

R_c represents alkoxy;

5 R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

R_g represents hydrogen, R_a or R_c.

10 106. A compound according to claim 105, wherein R_a groups in G are fluorine; R_c groups in G are methoxy and ethoxy; and R_d groups in G are methyl and ethyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/12153

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D209/42 C07D413/04 C07D209/52 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 11885 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); HUTCHISON ALAN (US)) 4 May 1995 see the whole document ---	1-106
E	WO 97 26243 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); LIU GANG (US); SHAW KENNETH (U) 24 July 1997 see the whole document -----	1-106

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1997	15.10.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatinal Application No

PCT/US 97/12153

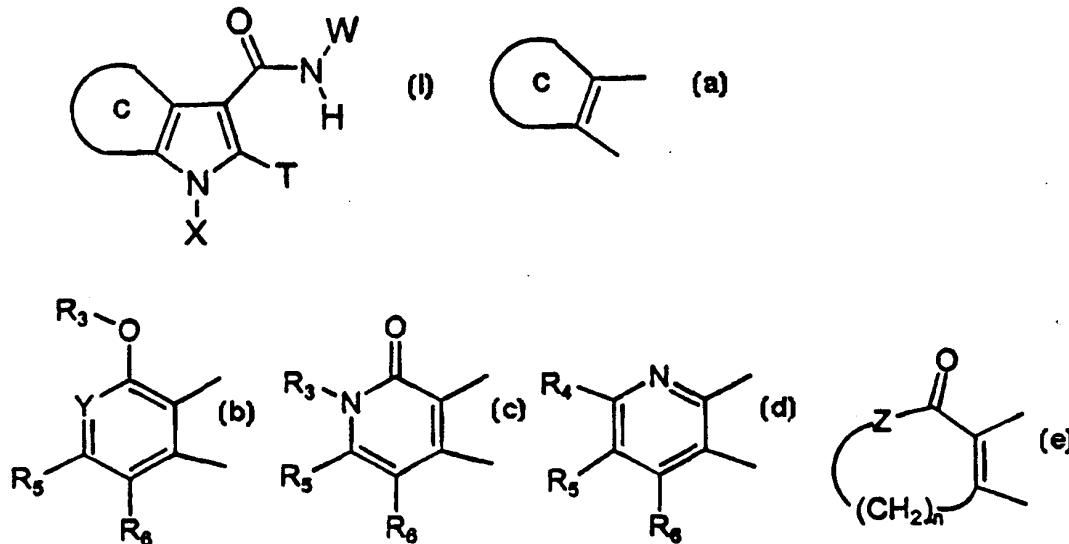
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511885 A	04-05-95	US 5484944 A AU 8126594 A CA 2175204 A CN 1143953 A CZ 9601129 A EP 0725775 A FI 961776 A HU 76064 A NO 961655 A PL 314136 A SE 9601563 A US 5608079 A	16-01-96 22-05-95 11-05-95 26-02-97 16-04-97 14-08-96 14-06-96 30-06-97 10-06-96 19-08-96 22-05-96 04-03-97
WO 9726243 A	24-07-97	NONE	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number:	WO 98/02420
C07D 209/42, 413/04, 209/52, A61K 31/40		(43) International Publication Date:	22 January 1998 (22.01.98)
(21) International Application Number:	PCT/US97/12153	(74) Agent:	NOONAN, Kevin, E.; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).
(22) International Filing Date:	14 July 1997 (14.07.97)	(81) Designated States:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority Data:	08/683,066 16 July 1996 (16.07.96) US	(71) Applicant (for all designated States except US):	NEUROGEN CORPORATION [US/US]; 35 Northeast Industrial Road, Branford, CT 06405 (US).
(60) Parent Application or Grant		(72) Inventors; and	
(63) Related by Continuation		(75) Inventors/Applicants (for US only):	ALBAUGH, Pamela [US/US]; 81 Long Hill Road, Clinton, CT 06413 (US). HUTCHISON, Alan [US/US]; 175 Bartlett Drive, Madison, CT 06443 (US). LIU, Gang [CN/US]; 144 Montoya Circle, Branford, CT 06405 (US).
US Filed on	08/683,066 (CIP) 16 July 1996 (16.07.96)	Published	With international search report.

(54) Title: CERTAIN FUSED PYRROLECARBOXANILIDES; A NEW CLASS OF GABA BRAIN RECEPTOR LIGANDS



(57) Abstract

The present invention encompasses structures of formula (I) or the pharmaceutically acceptable non-toxic salts thereof wherein (a) represents (b) or (c) or (d) or (e) wherein: W represents substituted or unsubstituted phenyl; X is hydrogen, hydroxy or lower alkyl; T is hydrogen, halogen, hydroxy, nitro, amino or alkyl; R₃ is hydrogen or an organic group; R₄ is hydrogen or substituted or unsubstituted organic substituent; R₅ and R₆ represent organic, and inorganic substituents; and n is 1, 2, 3, or 4, which compounds are highly selective agonists, antagonists or inverse agonists for GABA_A brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABA_A brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

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BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

**Certain Fused Pyrrolecarboxanilides; A New Class of
GABA Brain Receptor Ligands**

5

Field of the Invention

This invention relates to certain fused pyrrolecarboxanilides which selectively bind to GABA_A receptors. This invention also relates to pharmaceutical compositions comprising 10 such compounds. It further relates to the use of such compounds in treating anxiety, sleep and seizure disorders, and overdoses of benzodiazepine-type drugs, and enhancing alertness. The interaction of fused pyrrolecarboxanilides of the invention with a GABA binding site, the benzodiazepine (BDZ) receptor, is described. This interaction results in the pharmacological activities of these compounds.

15 **Description of the Related Art**

γ -Aminobutyric acid (GABA) is regarded as one of the major inhibitory amino acid transmitters in the mammalian brain. Over 30 years have elapsed since its presence in the brain was demonstrated (Roberts & Frankel, J. Biol. Chem. 187: 55-63, 1950; Udenfriend, J. Biol. Chem. 187: 65-69, 1950). Since that time, an enormous amount of effort has been 20 devoted to implicating GABA in the etiology of seizure disorders, sleep, anxiety and cognition (Tallman and Gallager, Ann. Rev. Neuroscience 8: 21-44, 1985). Widely, although unequally, distributed through the mammalian brain, GABA is said to be a transmitter at approximately 30% of the synapses in the brain. In most regions of the brain, GABA is associated with local inhibitory neurons and only in two regions is GABA associated with 25 longer projections. GABA mediates many of its actions through a complex of proteins localized both on cell bodies and nerve endings; these are called GABA_A receptors. Postsynaptic responses to GABA are mediated through alterations in chloride conductance that generally, although not invariably, lead to hyperpolarization of the cell. Recent investigations have indicated that the complex of proteins associated with postsynaptic GABA 30 responses is a major site of action for a number of structurally unrelated compounds capable

of modifying postsynaptic responses to GABA. Depending on the mode of interaction, these compounds are capable of producing a spectrum of activities (either sedative, anxiolytic, and anticonvulsant, or wakefulness, seizures, and anxiety).

1,4-Benzodiazepines continue to be among the most widely used drugs in the world.
5 Principal among the benzodiazepines marketed are chlordiazepoxide, diazepam, flurazepam, and triazolam. These compounds are widely used as anxiolytics, sedative-hypnotics, muscle relaxants, and anticonvulsants. A number of these compounds are extremely potent drugs; such potency indicates a site of action with a high affinity and specificity for individual receptors. Early electrophysiological studies indicated that a major action of benzodiazepines
10 was enhancement of GABAergic inhibition. The benzodiazepines were capable of enhancing presynaptic inhibition of a monosynaptic ventral root reflex, a GABA-mediated event (Schmidt et al., 1967, Arch. Exp. Path. Pharmakol. 258: 69-82). All subsequent electrophysiological studies (reviewed in Tallman et al. 1980, Science 207: 274-81, Haefley et al., 1981, Handb. Exptl. Pharmacol. 33: 95-102) have generally confirmed this finding, and
15 by the mid-1970s, there was a general consensus among electrophysiologists that the benzodiazepines could enhance the actions of GABA.

With the discovery of the "receptor" for the benzodiazepines and the subsequent definition of the nature of the interaction between GABA and the benzodiazepines, it appears that the behaviorally important interactions of the benzodiazepines with different neurotransmitter systems are due in a large part to the enhanced ability of GABA itself to modify these systems. Each modified system, in turn, may be associated with the expression
20 of a behavior.

Studies on the mechanistic nature of these interactions depended on the demonstration of a high-affinity benzodiazepine binding site (receptor). Such a receptor is present in the
25 CNS of all vertebrates phylogenetically newer than the boney fishes (Squires & Braestrup 1977, Nature 166: 732-34, Mohler & Okada, 1977, Science 198: 854-51, Mohler & Okada, 1977, Br. J. Psychiatry 133: 261-68). By using tritiated diazepam, and a variety of other compounds, it has been demonstrated that these benzodiazepine binding sites fulfill many of the criteria of pharmacological receptors; binding to these sites in vitro is rapid, reversible,
30 stereospecific, and saturable. More importantly, highly significant correlations have been shown between the ability of benzodiazepines to displace diazepam from its binding site and activity in a number of animal behavioral tests predictive of benzodiazepine potency (Braestrup & Squires 1978, Br. J. Psychiatry 133: 249-60, Mohler & Okada, 1977, Science 198: 854-51, Mohler & Okada, 1977, Br. J. Psychiatry 133: 261-68). The average therapeutic
2

doses of these drugs in man also correlate with receptor potency (Tallman et al. 1980, *Science* 207: 274-281).

In 1978, it became clear that GABA and related analogs could interact at the low affinity (1 mM) GABA binding site to enhance the binding of benzodiazepines to the 5 clonazepam-sensitive site (Tallman et al. 1978, *Nature*, 274: 383-85). This enhancement was caused by an increase in the affinity of the benzodiazepine binding site due to occupancy of the GABA site. The data were interpreted to mean that both GABA and benzodiazepine sites were allosterically linked in the membrane as part of a complex of proteins. For a number of 10 GABA analogs, the ability to enhance diazepam binding by 50% of maximum and the ability to inhibit the binding of GABA to brain membranes by 50% could be directly correlated. Enhancement of benzodiazepine binding by GABA agonists is blocked by the GABA receptor antagonist (+) bicuculline; the stereoisomer (-) bicuculline is much less active (Tallman et al., 1978, *Nature*, 274: 383-85).

Soon after the discovery of high affinity binding sites for the benzodiazepines, it was 15 discovered that a triazolopyridazine could interact with benzodiazepine receptors in a number of regions of the brain in a manner consistent with receptor heterogeneity or negative cooperativity. In these studies, Hill coefficients significantly less than one were observed in a number of brain regions, including cortex, hippocampus, and striatum. In cerebellum, triazolopyridazine interacted with benzodiazepine sites with a Hill coefficient of 1 (Squires et 20 al., 1979, *Pharma. Biochem. Behav.* 10: 825-30, Klepner et al. 1979, *Pharmacol. Biochem. Behav.* 11: 457-62). Thus, multiple benzodiazepine receptors were predicted in the cortex, hippocampus, striatum, but not in the cerebellum.

Based on these studies, extensive receptor autoradiographic localization studies were carried out at a light microscopic level. Although receptor heterogeneity has been 25 demonstrated (Young & Kuhar 1980, *J. Pharmacol. Exp. Ther.* 212: 337-46, Young et al., 1981 *J. Pharmacol Exp. Ther.* 216: 425-430, Niehoff et al. 1982, *J. Pharmacol. Exp. Ther.* 221: 670-75), no simple correlation between localization of receptor subtypes and the behaviors associated with the region has emerged from the early studies. In addition, in the cerebellum, where one receptor was predicted from binding studies, autoradiography revealed 30 heterogeneity of receptors (Niehoff et al., 1982, *J. Pharmacol. Exp. Ther.* 221: 670-75).

A physical basis for the differences in drug specificity for the two apparent subtypes of benzodiazepine sites has been demonstrated by Sieghart & Karobath, 1980, *Nature* 286: 285-87. Using gel electrophoresis in the presence of sodium dodecyl sulfate, the presence of several molecular weight receptors for the benzodiazepines has been reported. The receptors

were identified by the covalent incorporation of radioactive flunitrazepam, a benzodiazepine which can covalently label all receptor types. The major labeled bands have molecular weights of 50,000 to 53,000, 55,000, and 57,000 and the triazolopyridazines inhibit labeling of the slightly higher molecular weight forms (53,000, 55,000, 57,000) (Seighart et al. 1983, Eur. J. Pharmacol. 88: 291-99).

At that time, the possibility was raised that the multiple forms of the receptor represent "isoreceptors" or multiple allelic forms of the receptor (Tallman & Gallagher 1985, Ann. Rev. Neurosci. 8, 21-44). Although common for enzymes, genetically distinct forms of receptors have not generally been described. As we begin to study receptors using specific radioactive probes and electrophoretic techniques, it is almost certain that isoreceptors will emerge as important in investigations of the etiology of psychiatric disorders in people.

The GABAa receptor subunits have been cloned from bovine and human cDNA libraries (Schoenfield et al., 1988; Duman et al., 1989). A number of distinct cDNAs were identified as subunits of the GABAa receptor complex by cloning and expression. These are categorized into α , β , γ , δ , ϵ , and provide a molecular basis for the GABAa receptor heterogeneity and distinctive regional pharmacology (Shivvers et al., 1980; Levitan et al., 1989). The γ subunit appears to enable drugs like benzodiazepines to modify the GABA responses (Pritchett et al., 1989). The presence of low Hill coefficients in the binding of ligands to the GABAa receptor indicates unique profiles of subtype specific pharmacological action.

Drugs that interact at the GABAa receptor can possess a spectrum of pharmacological activities depending on their abilities to modify the actions of GABA. For example, the beta-carbolines were first isolated based upon their ability to inhibit competitively the binding of diazepam to its binding site (Nielsen et al., 1979, Life Sci. 25: 679-86). The receptor binding assay is not totally predictive about the biological activity of such compounds; agonists, partial agonists, inverse agonists, and antagonists can inhibit binding. When the beta-caroline structure was determined, it was possible to synthesize a number of analogs and test these compounds behaviorally. It was immediately realized that the beta-carbolines could antagonize the actions of diazepam behaviorally (Tenen & Hirsch, 1980, Nature 288: 609-10). In addition to this antagonism, beta-carbolines possess intrinsic activity of their own opposite to that of the benzodiazepines; they become known as inverse agonists.

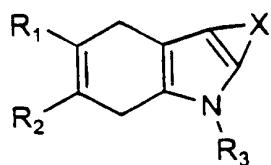
In addition, a number of other specific antagonists of the benzodiazepine receptor were developed based on their ability to inhibit the binding of benzodiazepines. The best studied of

these compounds is an imidazodiazepine (Hunkeler et al., 1981, *Nature* 290: 514-516). This compound is a high affinity competitive inhibitor of benzodiazepine and beta-carboline binding and is capable of blocking the pharmacological actions of both these classes of compounds. By itself, it possesses little intrinsic pharmacological activity in animals and 5 humans (Hunkeler et al., 1981, *Nature* 290: 514-16; Darragh et al., 1983, *Eur. J. Clin. Pharmacol.* 14: 569-70). When a radiolabeled form of this compound was studied (Mohler & Richards, 1981, *Nature* 294: 763-65), it was demonstrated that this compound would interact with the same number of sites as the benzodiazepines and beta-carbolines, and that the interactions of these compounds were purely competitive. This compound is the ligand of 10 choice for binding to GABAa receptors because it does not possess receptor subtype specificity and measures each state of the receptor.

The study of the interactions of a wide variety of compounds similar to the above has led to the categorizing of these compounds. Presently, those compounds possessing activity similar to the benzodiazepines are called agonists. Compounds possessing activity opposite to 15 benzodiazepines are called inverse agonists, and the compounds blocking both types of activity have been termed antagonists. This categorization has been developed to emphasize the fact that a wide variety of compounds can produce a spectrum of pharmacological effects, to indicate that compounds can interact at the same receptor to produce opposite effects, and to indicate that beta-carbolines and antagonists with intrinsic anxiogenic effects are not 20 synonymous.

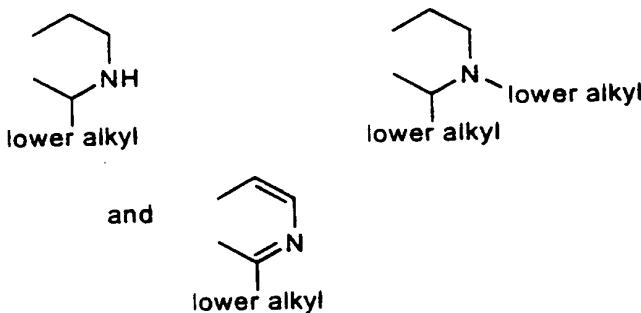
A biochemical test for the pharmacological and behavioral properties of compounds that interact with the benzodiazepine receptor continues to emphasize the interaction with the GABAergic system. In contrast to the benzodiazepines, which show an increase in their affinity due to GABA (Tallman et al., 1978, *Nature* 274: 383-85, Tallman et al., 1980, *Science* 207: 274-81), compounds with antagonist properties show little GABA shift (i.e., change in 25 receptor affinity due to GABA) (Mohler & Richards 1981, *Nature* 294: 763-65), and the inverse agonists actually show a decrease in affinity due to GABA (Braestrup & Nielson 1981, *Nature* 294: 472-474). Thus, the GABA shift predicts generally the expected behavioral properties of the compounds.

30 Various compounds have been prepared as benzodiazepine agonists and antagonists. For Example, U.S. Patents Nos. 3,455,943, 4,435,403, 4,596,808, 4,623,649, and 4,719,210, German Patent No. DE 3,246,932, and Liebigs Ann. Chem. 1986, 1749 teach assorted benzodiazepine agonists and antagonists and related anti-depressant and central nervous system active compounds. U.S. Patent No. 3,455,943 discloses compounds of the formula:



wherein R₁ is a member of the group consisting of hydrogen and lower alkoxy; R₂ is a member of the group consisting of hydrogen and lower alkoxy; R₃ is a member of the group consisting of hydrogen and lower alkyl; and X is a divalent radical selected from the group consisting of

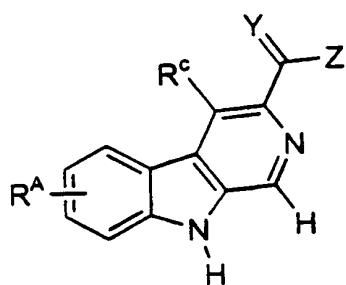
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and the non-toxic acid addition salts thereof.

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U.S. Patent No. 4,435,403 teaches compounds of the formula:

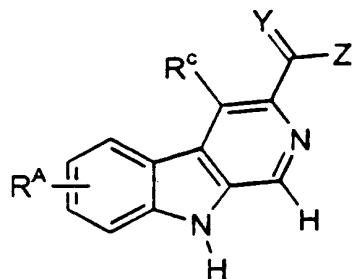


wherein

R^C is hydrogen, lower alkyl, alkoxyalkyl of up to 6 C-atoms, cycloalkyl of 3-6 C-atoms, arylalkyl of up to 8 C-atoms, or (CH₂)_nOR₁₈ wherein R₁₈ is alkyl of up to 6 C-atoms, cycloalkyl of 3-6 C-atoms or arylalkyl of up to 8 C-atoms and n is an integer of 1 to 3; Y is oxygen, two hydrogen atoms or NOR₁, wherein R₁ is hydrogen, lower alkyl, aryl or arylalkyl of up to 6 C-atoms, COR₂, wherein R₂ is lower alkyl of up to 6 C-atoms, or Y is CHCOOR₃, wherein R₃ is hydrogen or lower alkyl or Y is NNR₄R₅, wherein R₄ and R₅ can be the same or different and each is hydrogen, lower alkyl, C₆-10-aryl, C₇-10-arylalkyl or CONR₆R₇.
15

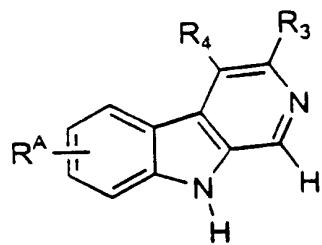
wherein R₆ and R₇ can be the same or different and each is hydrogen or lower alkyl, or R₄ and R₅ together with the connecting N-atom, form a 5- or 6-membered heterocyclic ring which optionally may also contain an O-atom or up to 3 N-atoms and which optionally may be substituted by a lower alkyl group; Z is hydrogen, or alkoxy or aralkoxy each of up to 10 C-atoms and each optionally substituted by hydroxy, or Z is alkyl of up to 6 C-atoms, C₆-10-aryl or C₇-10-arylalkyl each of which may optionally be substituted by a COOR₈ or a CONR₉R₁₀ group, wherein R₈ is alkyl of up to 6 C-atoms, and R₉ and R₁₀ can be the same or different and each is hydrogen or alkyl of up to 6 C-atoms; or Z is NR₉R₁₀, wherein R₉ and R₁₀ are as defined above; or Z is NR₁₁CHR₁₂R₁₃, wherein R₁₁ and R₁₂ each is hydrogen or together form a N=C double bond, wherein R₁₃ is C₁-10-alkyl or NR₁₄R₁₅, wherein R₁₄ and R₁₅ are the same or different and each is hydrogen, OH or alkyl or alkoxy each of up to 6 C-atoms, or wherein R₁₂ and R₁₃ together are oxygen, in which case, R₁₁ is hydrogen; or Z is COOR₂ wherein R₂ is as defined above; or Y and Z, together with the connecting C-atom, may form a 5- or 6-membered heterocyclic ring which contains an O-atom, adjoining O- and N-atoms or up to 4 N atoms and which optionally may be substituted by a lower alkyl group, hydroxy or oxo.

U.S. Patent No. 4,596,808 discloses compounds of the formula:

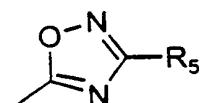


wherein R^A is H, F, Cl, Br, I, NO₂, CN, CH₃, CF₃, SCH₃, NR₁₆R₁₇ or NHCOR₁₆, wherein R₁₆ of R₁₇ are the same or different and each is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 C-atoms, arylalkyl or cycloalkyl each of up to 10 C-atoms, or wherein R₁₆ and R₁₇ together form a saturated or unsaturated 3-7 membered heterocyclic ring.

U.S. Patent No. 4,623,649 teaches compounds of the formula:

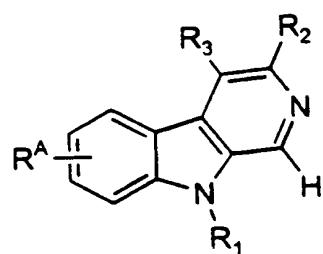


wherein R₃ is an oxadiazolyl residue of the formula



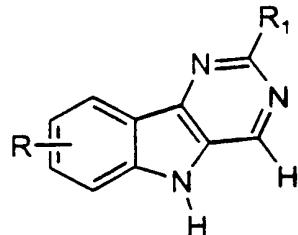
wherein R₅ stands for lower alkyl of up to 3 carbon atoms or an ester -CO₂R₆ with R₆ being hydrogen or lower alkyl of up to 3 carbon atoms, R₄ is hydrogen, lower alkyl of up to 3 carbon atoms, or CH₂OR₉ wherein R₉ is lower alkyl of up to 3 carbon atoms, R^A is phenyl or a hydrocarbon residue containing 2-10 carbon atoms which can be cyclic or acyclic, saturated or unsaturated, branched or unbranched, and which can optionally be substituted by oxo, formyl OH, O-alkyl of up to 3 carbon atoms or phenyl, and wherein in a cyclic hydrocarbon residue, a CH₂-group can be replaced by oxygen.

U.S. Patent No. 4,719,210 discloses compounds of the formula:



wherein R₁ is hydrogen or a protecting group, R₂ is -CH=CR₄ or -C=CR₄, R₄ is hydrogen or halogen, R₃ is hydrogen, lower alkyl or lower alkoxyalkyl, R^A is, *inter alia*, hydrogen, OR₇, lower alkyl, which optionally is substituted with aryl, lower alkoxy or NR₅R₆, R₅ and R₆ can be the same or different and in each case is hydrogen, lower alkyl or together with the nitrogen atom a 5-6 member ring, which can contain another heteroatom. R₇ is lower alkyl, optionally substituted aryl or arylalkyl, and each compound can contain one or more R^A radicals which are not hydrogen.

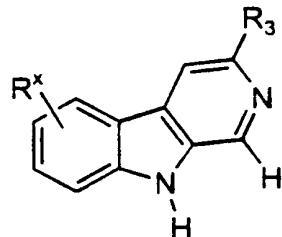
German Patent No. DE 3,246,932 discloses compounds of the formula:



wherein

- 5 R = halogen, NO₂, CO₂H, modified CO₂H, R₂O, R₂S(O)_n; n = 0-2; and R₁ = H, alkyl, cycloalkyl, arylalkyl, aryl, CO₂H, amino, R₂O, R₂S(O)_n.

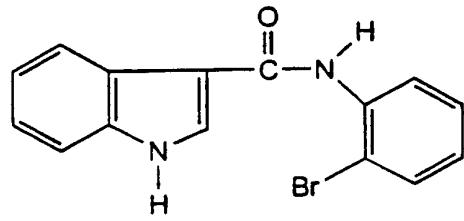
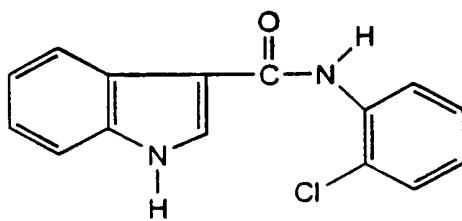
Liebigs Ann. Chem. 1986, 1749-1764 teaches compounds of the formula:

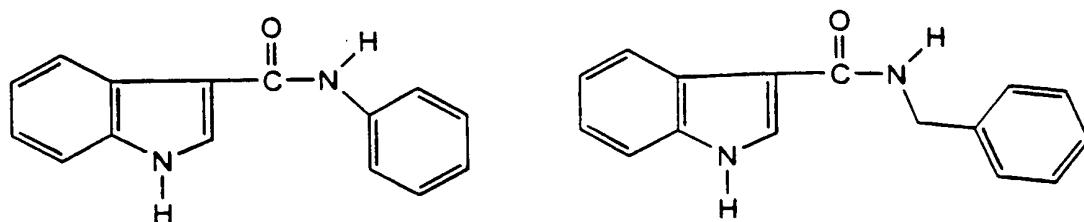


- 10 where R^X is hydrogen, methyl, benzyloxy, or methoxy, and R₃ is carboethoxy.

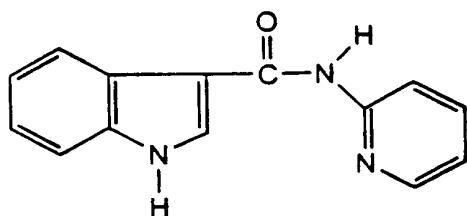
None of these compounds are indole-3-carboxamides and no such compounds displaying activity at GABA receptors have been described.

A variety of indole-3-carboxamides are described in the literature. For example, J. Org. Chem., 42: 1883-1885 (1977) discloses the following compounds.





J. Heterocyclic Chem., 14: 519-520 (1977) discloses a compound of the following formula:



5

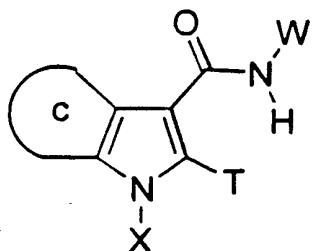
None of these indole-3-carboxamides includes an oxy substituent at the 4-position of the indole ring.

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SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABA_A binding site, the benzodiazepine receptor.

The invention provides pharmaceutical compositions comprising compounds of Formula I. The invention also provides compounds useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. Accordingly, a broad embodiment of the invention is directed to compounds of general Formula I:



I

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or the pharmaceutically acceptable non-toxic salts thereof wherein:

T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;

X is hydrogen, hydroxyl or lower alkyl;

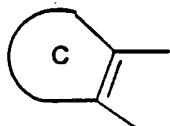
W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups

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independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having

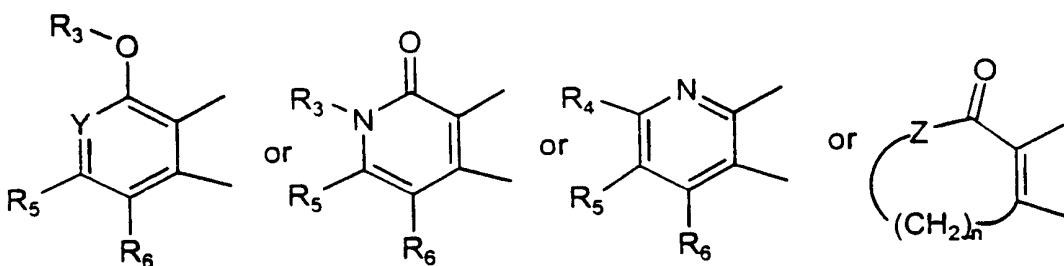
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3-7 carbon atoms; and



represents

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wherein:

Y represents nitrogen or C-R4;

Z represents N-R7 or a carbon atom substituted with R8 and R9, i.e., C(R8)(R9);

5

n is 1, 2, 3, or 4;

R3 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R4 is halogen or trifluoromethyl; or

-OR10, -COR10, -CO₂R10, -OCOR10, or -R10, where R10 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

-CONR11R12 or -(CH₂)_mNR11R12, where m is 0, 1, or 2; R11 represents hydrogen, lower alkyl; and R12 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR11R12 forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

15

R5 and R6 are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy;

R7 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

20

R8 is hydrogen or lower alkyl; and

R9 is -COR13, -CO₂R13 or -R13, where R13 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

25

R9 is -CONR14R15 or -(CH₂)_kNR14R15, where k is 0, 1, or 2; R14 represents hydrogen, lower alkyl; and R15 is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is

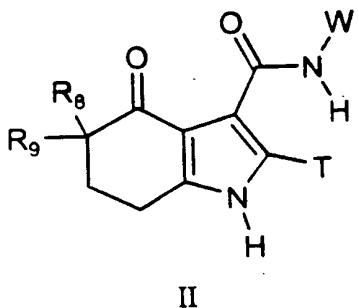
lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. In other words, while the compounds of the invention all interact with GABAa brain receptors, they do not display identical physiologic activity. Thus, these compounds are useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. For example, these compounds can easily be used to treat overdoses of benzodiazepine-type drugs as they would competitively bind to the benzodiazepine receptor.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

In addition, the present invention encompasses compounds of Formula II.

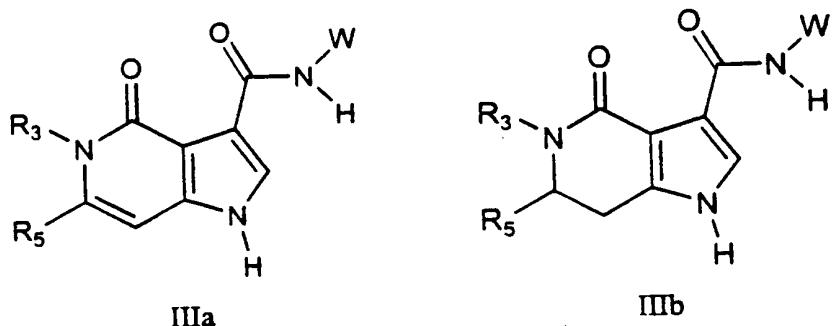


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or the pharmaceutically acceptable non-toxic salts thereof wherein W, T, R8 and R9 are as defined above.

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The present invention also encompasses compounds of Formula IIIa and IIIb:

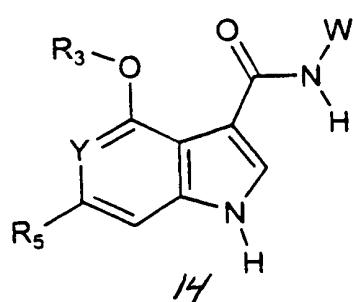


or the pharmaceutically acceptable non-toxic salts thereof wherein W, R3, and R5 are as defined above.

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Preferred compounds of Formula IIIb are those where R3 is hydrogen or alkyl; and R5 is hydrogen.

The present invention also encompasses compounds of Formula IV:

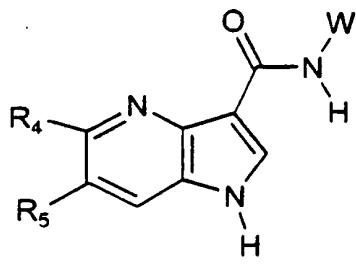


IV

or the pharmaceutically acceptable non-toxic salts thereof wherein W, Y, R₃, and R₅ are defined above.

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The present invention also encompasses compounds of Formula V:

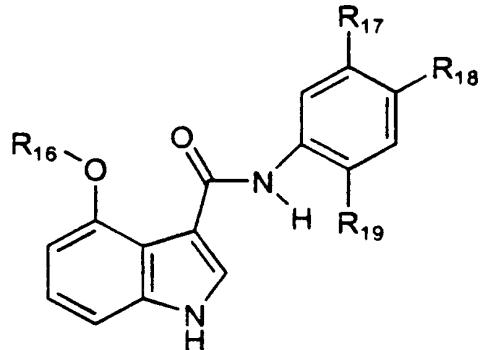


V

or the pharmaceutically acceptable non-toxic salts thereof wherein W, R₄, and R₅ are defined above.

10

The invention further encompasses compounds of Formula VI:



VI

15

or the pharmaceutically acceptable non-toxic salts thereof wherein:

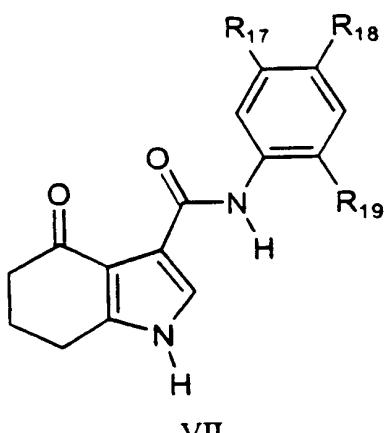
R₁₆ is hydrogen, benzyl or lower alkyl;

R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and R₁₉ is hydrogen, hydroxyl, or halogen.

5

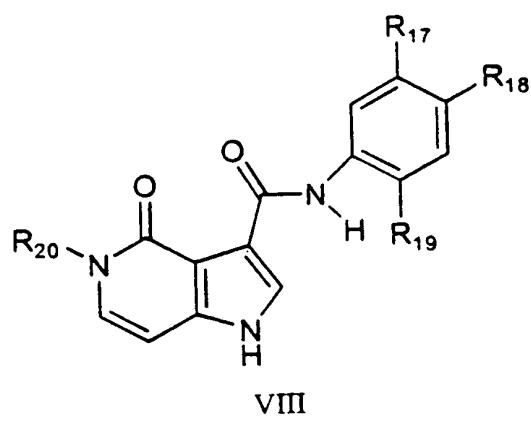
The invention additionally encompasses compounds of Formula VII:



10

or the pharmaceutically acceptable non-toxic salts thereof where R₁₇, R₁₈ and R₁₉ are defined above.

The invention further encompasses compounds of Formula VIII:

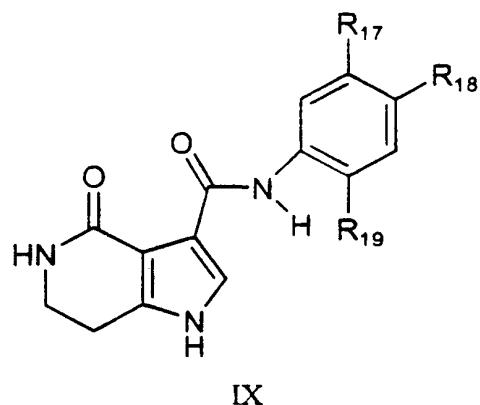


15

where R₁₇, R₁₈, and R₁₉ are defined above and R₂₀ is hydrogen or alkyl.

The invention further encompasses compounds of Formula IX:

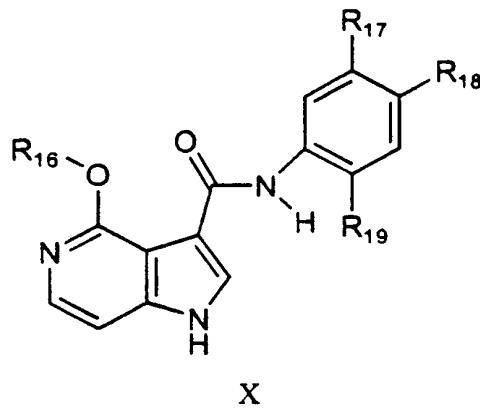
16



where R₁₇, R₁₈, and R₁₉ are defined above.

5

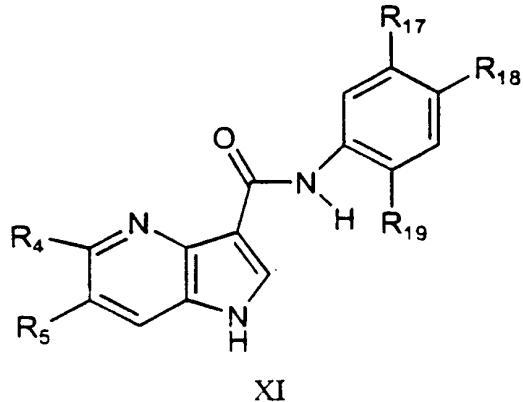
The invention further encompasses compounds of Formula X:



where R₁₆, R₁₇, R₁₈, and R₁₉ are defined above.

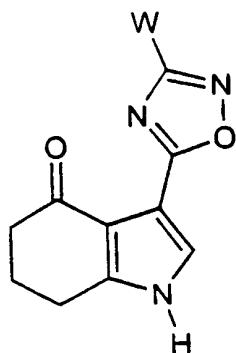
10

The invention further encompasses compounds of Formula XI:



where R₄, R₅, R₁₇, R₁₈, and R₁₉ are defined above.

The invention further encompasses compounds of Formula XII:

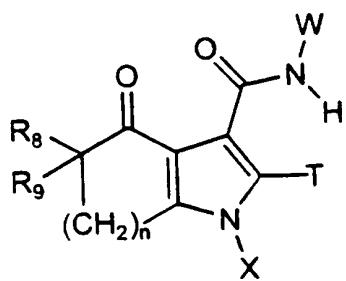


XII

5 wherein W represents phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl or 6-quinolinyl, each of which may be mono or disubstituted with halogen, cyano, hydroxy, lower alkyl, amino, mono or dialkylamino where each alkyl is independently lower alkyl, lower alkoxy, or NR₁COR₂, COR₂, CONR₁R₂ or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen or lower alkyl.

10

Further, the present invention provides compounds of Formula XIII:



XIII

wherein W, R₈ and R₉ are as defined above;

15 T represents hydrogen, amino, or nitro;

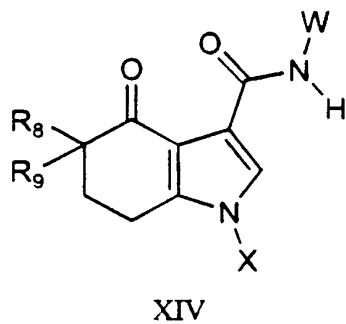
X is alkyl or hydrogen; and

n is 1 or 2.

A preferred group of compounds of Formula XIII are those where R₈ and R₉ are independently alkyl or hydrogen; and n is 1. Another preferred group of compounds of Formula XIII are those where R₈ and R₉ are independently alkyl or hydrogen; and n is 2.

Particularly preferred compounds of Formula XIII where n is 2 are those where R₈ and R₉ are hydrogen; and X and T are both hydrogen.

The invention also provides compounds of Formula XIV:



5

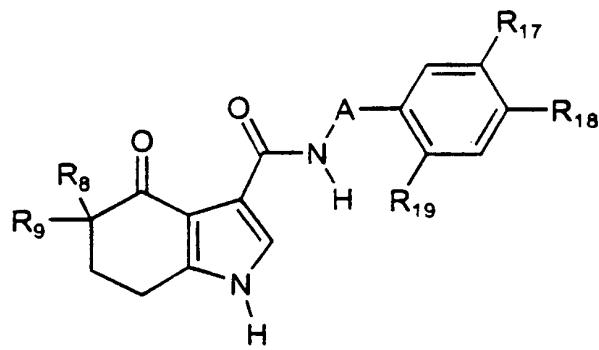
wherein W is as defined above;

R₈ and R₉ are independently alkyl or hydrogen; and

X is hydrogen, methyl, or ethyl.

10 Preferred compounds of Formula XIV are those where R₈ and R₉ are both hydrogen and X is hydrogen.

The present invention further provides compounds of Formula XV.



15

R₈ and R₉ are as defined above;

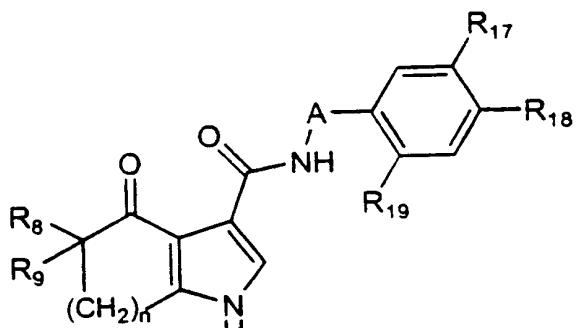
A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

20 R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and
R₁₉ is hydrogen, hydroxyl, or halogen.

5

The present invention also encompasses compounds of Formula XVI.



XVI

R₈ and R₉ are as defined above;

10 A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

n is 1 or 2;

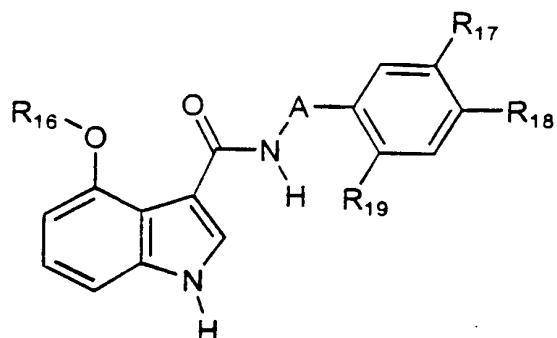
R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

15 R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂, CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and

R₁₉ is hydrogen, hydroxyl, or halogen.

20

Further, the present invention provides compounds of Formula XVII.



XVII

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

5 R₁₆ is hydrogen, benzyl, or lower alkyl;

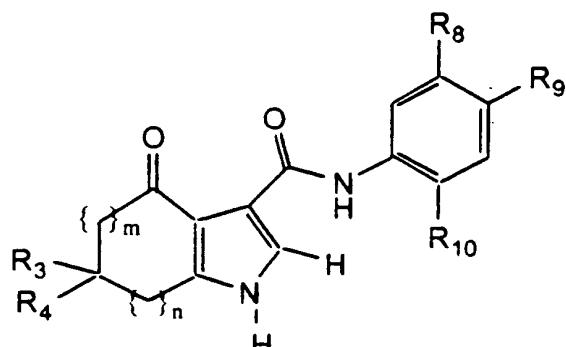
R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where

10 each alkyl is independently straight or branched chain lower alkyl, NR_1COR_2 , COR_2 , CO_2R_2 where R_1 and R_2 are as defined above, cyano, or halogen; and

R₁₉ is hydrogen, hydroxyl, or halogen.

In addition, the present invention encompasses compounds of Formula DII.



DII

wherein

R_3 and R_4 are the same or different and represent hydrogen, alkyl, COR_5 or CO_2R_5 where

R_5 is alkyl or cycloalkyl having 3-7 carbon atoms, CONR_6R_7 where R_6 and R_7 are

20 selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms,

phenyl, 2-,3-, or 4-pyridyl, or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms;

R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

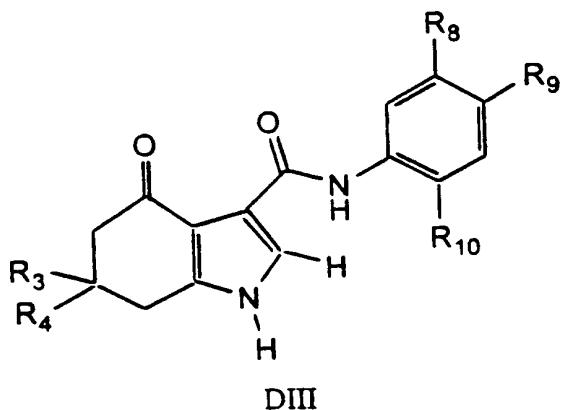
10 R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen.

15 In addition, the present invention encompasses compounds of Formula DIII.



wherein

20 R₃ and R₄ are the same or different and represent hydrogen or alkyl;

R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

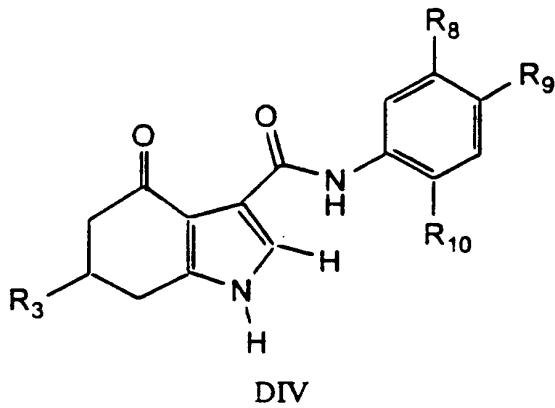
R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIII are those where the phenyl group is mono-, di-, or trisubstituted in the 2,4, and/or 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen. Particularly preferred compounds of Formula DIII are those where the phenyl group is trisubstituted in the 2,4, and 5 positions relative to the point of attachment of the phenyl ring to the amide nitrogen, and R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DIV.



wherein

R₃ represents alkyl;

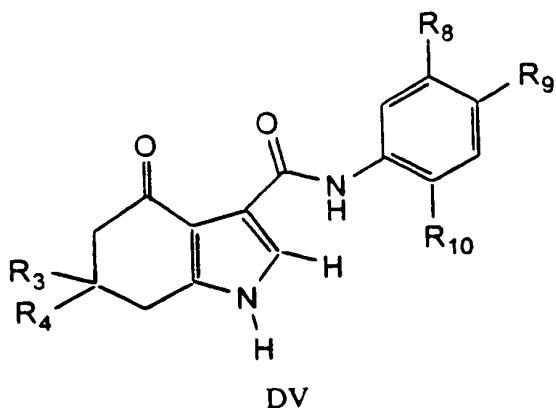
R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R9 is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

Preferred compounds of Formula DIV are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DV.



wherein

R₃ and R₄ are the same or different and represent alkyl;

5 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms,

amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

10

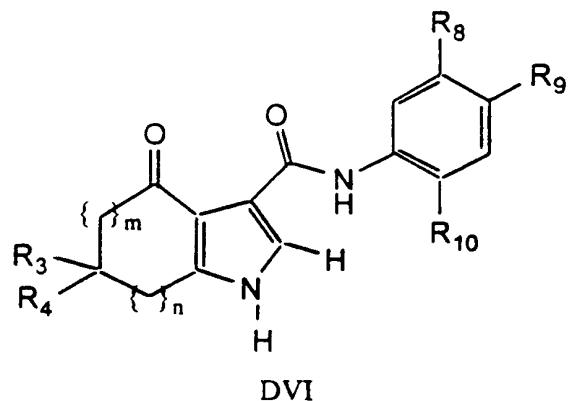
R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino.

15

Preferred compounds of Formula DV are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen. Particularly preferred compounds of Formula DV are those where R₃ and R₄ are both methyl, and R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

20

In addition, the present invention encompasses compounds of Formula DVI



wherein

q is an integer of from 2-6;

5 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

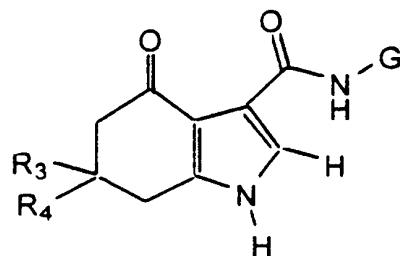
10 R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

Preferred compounds of Formula DVI are those where R₈, R₉, and R₁₀ are independently selected from hydrogen, halogen, hydroxy, alkoxy, and alkyl, provided that not all of R₈, R₉, and R₁₀ are hydrogen.

In addition, the present invention encompasses compounds of Formula DVII.



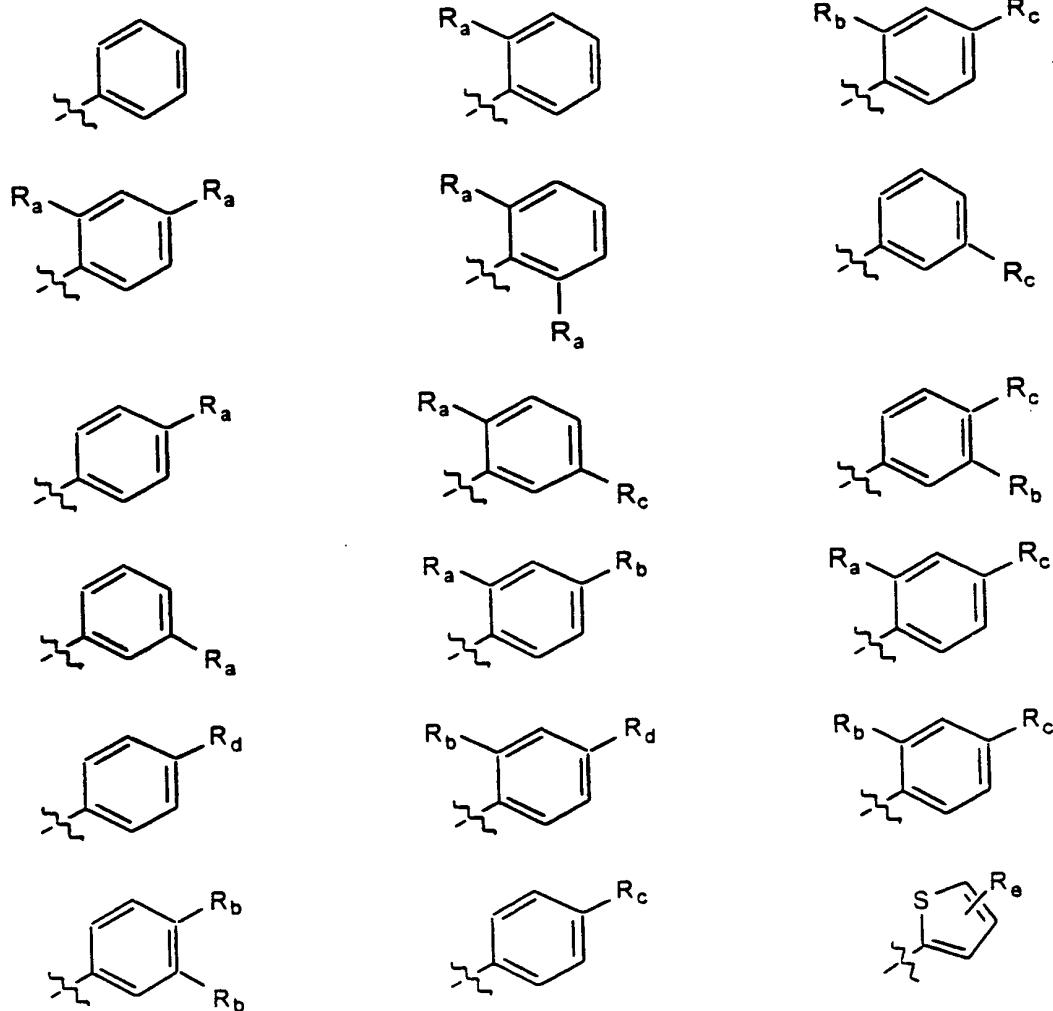
where

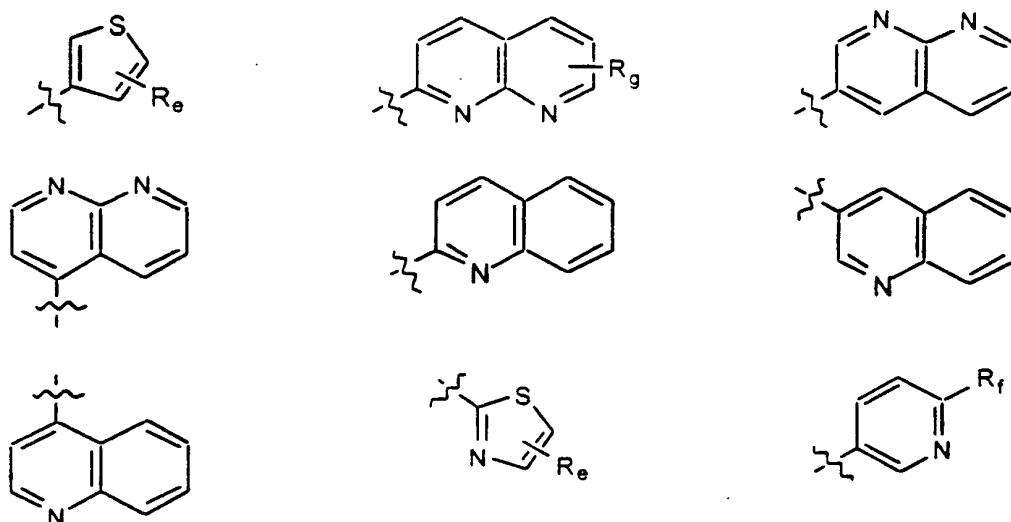
G represents aryl or heteroaryl such as, for example, thienyl, thiazolyl, pyridyl, naphthyridinyl, quinolinyl, or phenyl, each of which is optionally mono-, di- or trisubstituted with halogen alkyl alkoxy, or hydroxy; and

- 5 R₃ and R₄ are the same or different and represent hydrogen or alkyl, provided that not both R₃ and R₄ are hydrogen.

Preferred compounds of Formula DVII are those where R₃ and R₄ are C₁-3 alkyl, and more preferably methyl. Other preferred compounds of Formula DVII are those where R₃ is hydrogen and R₄ is C₁-3 alkyl, and more preferably R₄ is methyl.

- 10 Preferred compounds of Formula DVII include a G group selected from the following:





In the above G groups, the following definitions apply:

R_a is halogen;

R_b is hydroxy;

5 R_c represents alkoxy;

R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

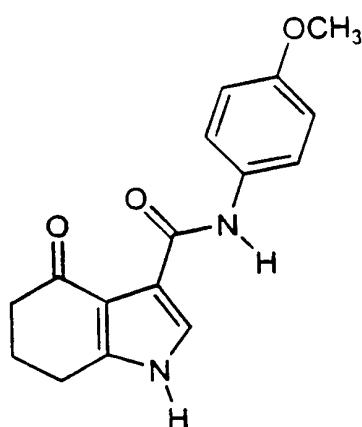
R_g represents hydrogen, R_a or R_c.

10 In those formulas where more than one of the same substituent appears, those substituents are the same or different.

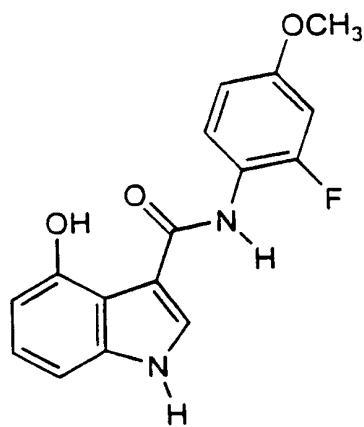
Particularly preferred R_a groups in G are fluorine. Particularly preferred R_c groups in G are methoxy and ethoxy. Particularly preferred R_d groups in G are methyl and ethyl.

15 Representative compounds of the invention are shown below in Table 1.

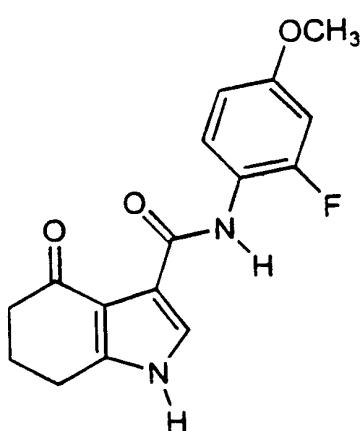
Table 1



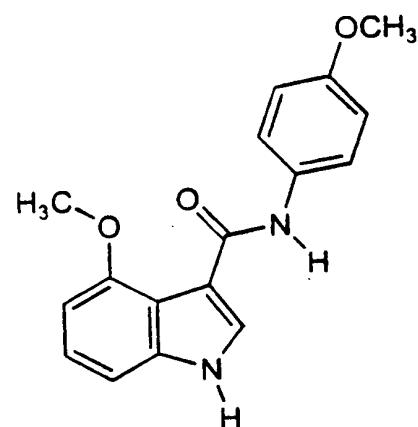
Compound 1



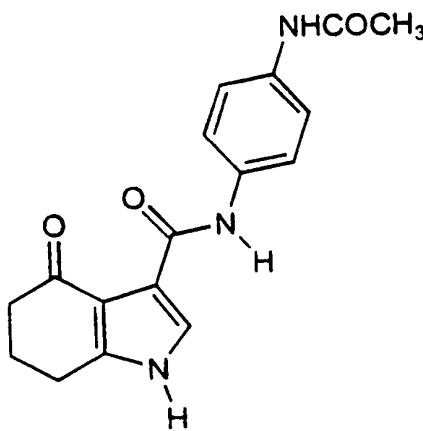
Compound 2



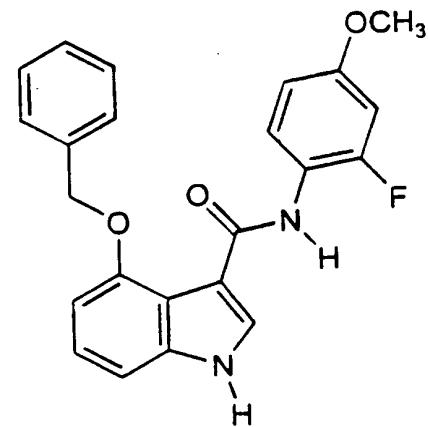
Compound 6



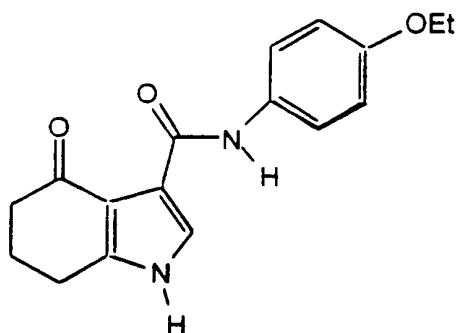
Compound 8



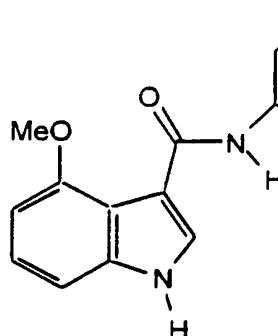
Compound 12



Compound 14

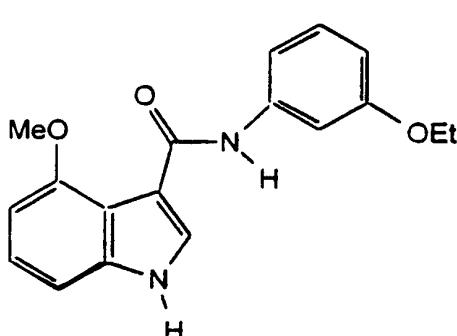


Compound 3

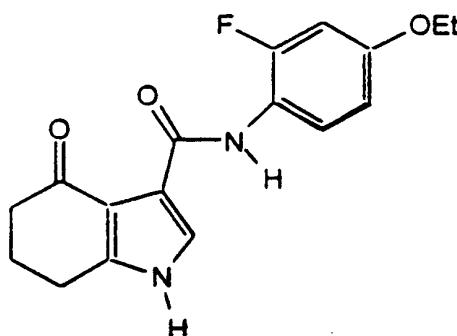


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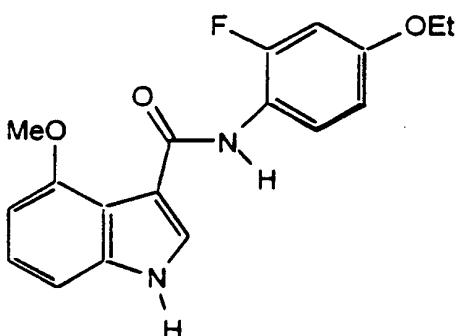
Compound 4



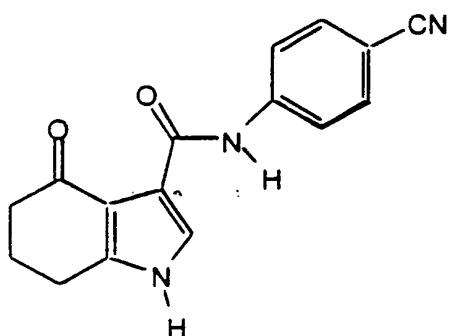
Compound 5



Compound 7

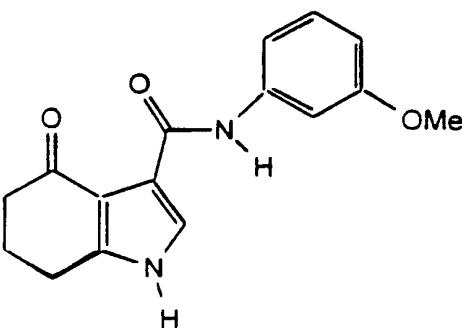


Compound 9

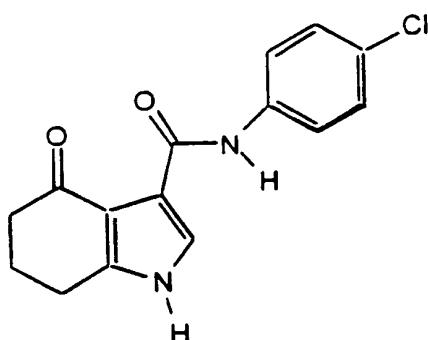


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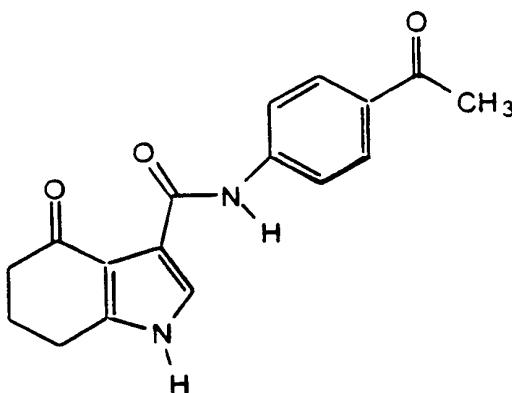
Compound 10



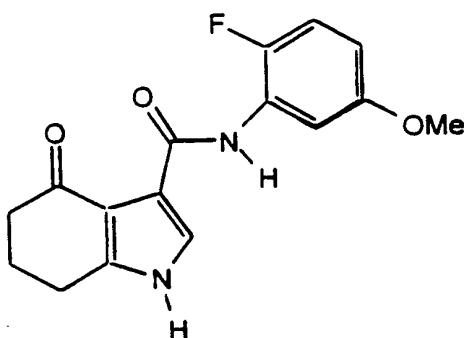
Compound 11



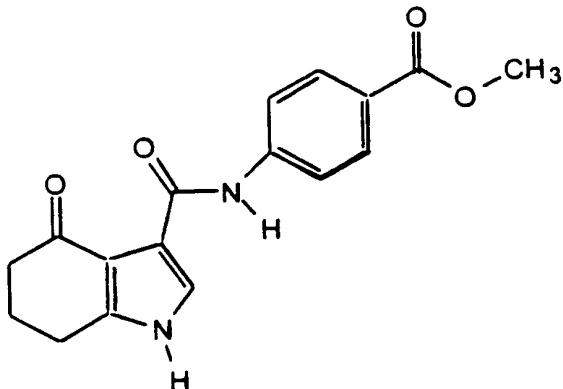
Compound 13



Compound 15

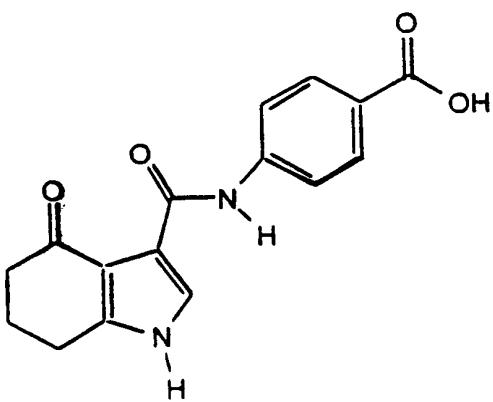


Compound 16

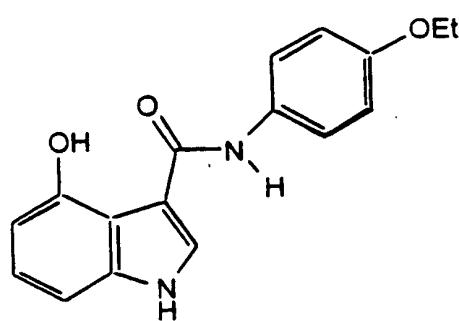


Compound 17

5



Compound 18



Compound 19

10

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfonic, formic, toluenesulfonic,
30 hydrochloric, phosphoric, hydrobromic, sulfuric, sulfonic, formic, toluenesulfonic,

methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-(CH₂)_n-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the prodrugs, preferably acylated prodrugs, of 5 the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

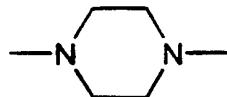
By "alkyl" and "lower alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, 10 isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "phenylalkyl" as used herein is meant a phenyl group covalently bonded to an alkyl group as defined above and the alkyl group is covalently bonded to another moiety, such as, for example, a nitrogen atom.

15 By "alkoxy" and "lower alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxyl, neopentoxyl, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

20 By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "N-alkylpiperazyl" in the invention is meant radicals of the formula:



where R is a lower alkyl as defined above.

25 By "monoalkylamino" as used herein is meant an amino substituent substituted with one (1) alkyl group where the alkyl group is lower alkyl as defined above.

By "dialkylamino" as used herein is meant an amino substituent substituted with two (2) alkyl groups where the alkyl groups are independently lower alkyl groups as defined above.

30 By "alkylenedioxy" as used herein is meant a group of the formula -O-A-O- where A represents C₁-C₃ alkylene optimally substituted with up to two C₁-C₂ alkyl groups and each oxygen atom is covalently bound to the aromatic ring, i.e., the phenyl group. The oxygen

atoms of such alkylenedioxy groups are typically attached to adjacent carbon atoms of the aromatic ring.

The pharmaceutical utility of compounds of this invention are indicated by the following assay for GABA_A receptor binding activity.

5 Assays are carried out as described in Thomas and Tallman (J. Bio. Chem. 156: 9838-9842, J. Neurosci. 3: 433-440, 1983). Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of 0.05 M Tris HCl buffer (pH 7.4 at 4°C). The tissue homogenate is centrifuged in the cold (4°) at 20,000 x g for 20'. The supernatant is decanted and the pellet is rehomogenized in the same volume of buffer and again centrifuged at 20,000 x g. The 10 supernatant is decanted and the pellet is frozen at -20°C overnight. The pellet is then thawed and rehomogenized in 25 volume (original wt/vol) of buffer and the procedure is carried out twice. The pellet is finally resuspended in 50 volumes (w/vol of 0.05 M Tris HCl buffer (pH 7.4 at 40°C).

15 Incubations contain 100 ml of tissue homogenate, 100 ml of radioligand 0.5 nM (³H-RO15-1788 [³H-Flumazenil] specific activity 80 Ci/mmol), drug or blocker and buffer to a total volume of 500 ml. Incubations are carried for 30 min at 4°C then are rapidly filtered through GFB filters to separate free and bound ligand. Filters are washed twice with fresh 0.05 M Tris HCl buffer (pH 7.4 at 4°C) and counted in a liquid scintillation counter. 1.0 mM diazepam is added to some tubes to determine nonspecific binding. Data are collected in triplicate determinations, averaged and % inhibition of total specific binding is calculated. Total Specific Binding = Total - Nonspecific. In some cases, the amounts of unlabeled drugs 20 is varied and total displacement curves of binding are carried out. Data are converted to K_i values. Representative data for compounds of this invention are listed in Tables 2 and 3.

Table 2

<u>Compound Number</u>	<u>K_i(nM)</u>
1	4
2	430
6	1
8	25
12	28
14	133

Table 3

<u>Compound Number</u>	<u>K_i(nM)</u>
22	53
26	3
30	10
35	2
46	3
62	0.8
72	26
74	18
80	31
81	14
86	2
93	6
96	29
102	37

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic

pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended

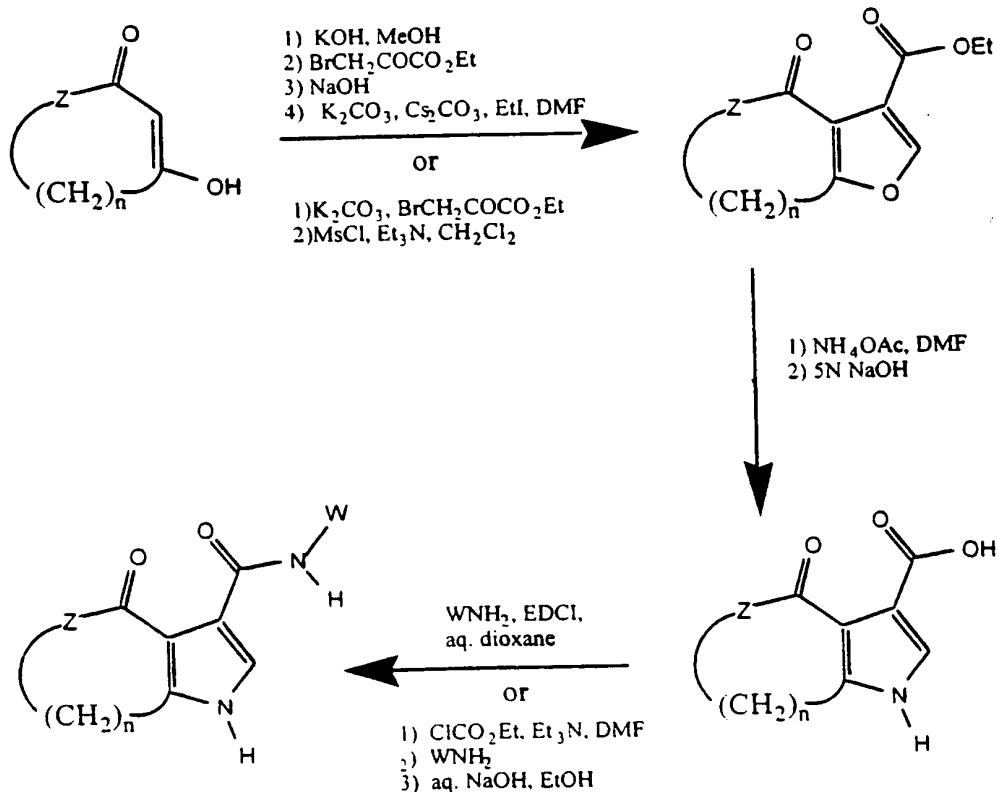
or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

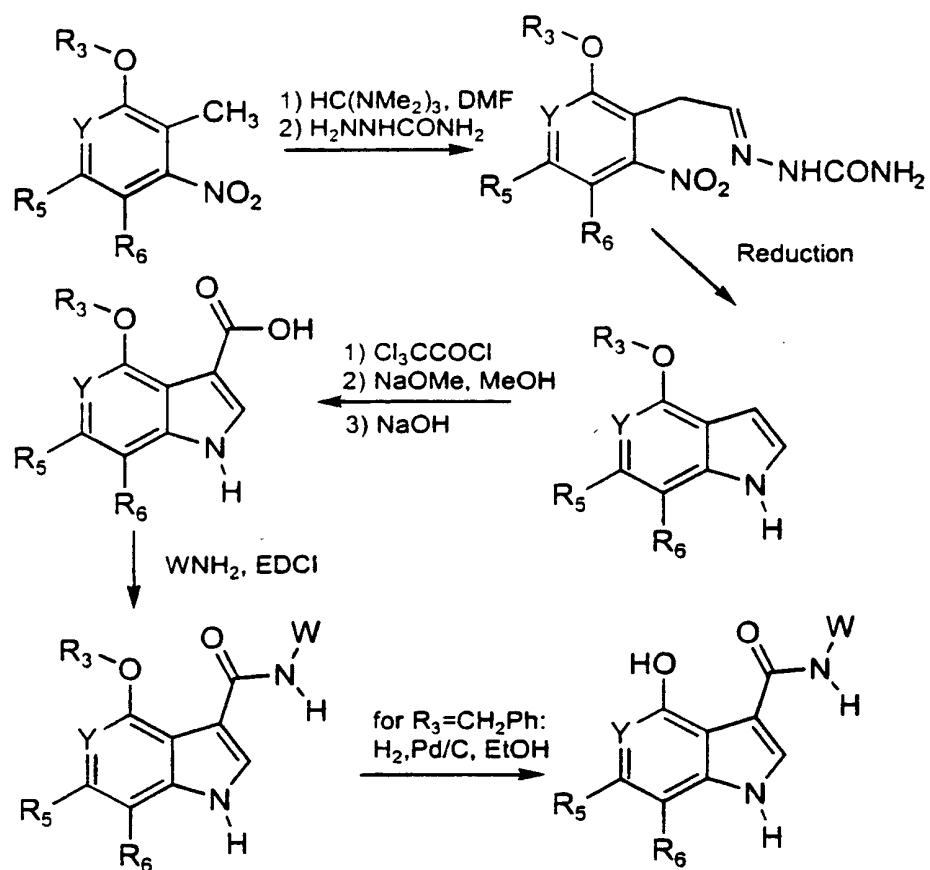
An illustration of the preparation of compounds of the present invention is given in Schemes I and II.

Scheme I



where W, Z, and n are as defined above.

Scheme II



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Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples. In some cases protection of certain reactive functionalities may be necessary to achieve some of the above transformations. In general the need for such protecting groups will be apparent to those skilled in the art of organic synthesis as well as the conditions necessary to attach and remove such groups.

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The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures described in them.

Example 1

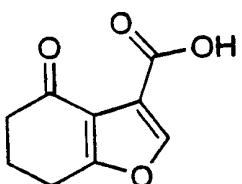
Preparation of starting materials and intermediates

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known synthetic methods.

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Representative examples of methods for preparing intermediates of the invention are set forth below.

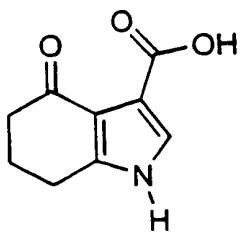
1. 4-Oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid



10 4-Oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid was prepared as follows: To a stirred solution of potassium hydroxide (28.06 g, 0.5 mol) in methyl alcohol (100 mL) under nitrogen at 0°C was added dropwise a solution of cyclohexanedione (56.07 g, 0.5 mol) in methyl alcohol (100 mL). The mixture was stirred at 0°C for 0.5 h, then a solution of ethyl bromopyruvate (66 mL, 0.525 mol) in methyl alcohol (100 mL) was added dropwise. After allowing the mixture to stir at ambient temperature for 17 h, a 50% aqueous sodium hydroxide solution (60 mL) was added dropwise and stirring continued an additional 7 h. After dilution with water, the solution was acidified and the methanol removed *in vacuo*. Ice water was added and the precipitate filtered and dried *in vacuo* to afford 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid. m.p. 137-138 °C.

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20 2. 4-Oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid

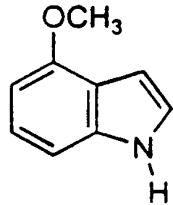


To a stirred suspension of 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylic acid (28.2 g, 157 mmol) in ethyl alcohol (500 mL) under nitrogen at ambient temperature was added acetyl chloride (56 mL, 783 mmol) dropwise. After stirring 1 h, the solution was then heated

at reflux for 1 h. The solution was cooled and concentrated *in vacuo*. The residue was taken up into dichloromethane, washed with aqueous sodium bicarbonate, washed quickly with 1N sodium hydroxide, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford ethyl 4-oxo-4,5,6,7-tetrahydrobenzofuran-3-carboxylate as an oil. A mixture of this ester (24.46 g, 117 mmol) and ammonium acetate (15.85 g, 206 mmol) in N,N-dimethylformamide (225 mL) was heated at 100° C under nitrogen for 1.25 h. The mixture was cooled, poured into ice water, and extracted two times with dichloromethane. The combined organic extracts were washed with water, dried over magnesium sulfate, filtered, concentrated *in vacuo*, and the residue triturated with ether to give ethyl 4-oxo-4,5,6,7-tetrahydroindole-3-carboxylate. A mixture of this ester (11.31 g, 55 mmol) in 5N sodium hydroxide (200 mL) and ethanol (20 mL) was heated at reflux for 1 h. After cooling in an ice bath, the mixture was acidified with concentrated hydrochloric acid, the precipitate filtered, rinsed with ice water, and dried *in vacuo* to afford 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid. m.p. 269-270°C.

3. 4-Oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (m.p. 225-228 °C) is prepared essentially according to the procedure set forth in Example 1 and part 1 of this example.

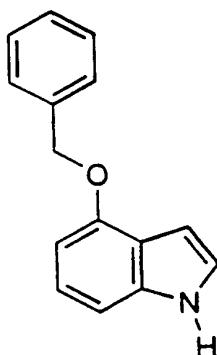
4. 4-Methoxy-1H-indole



A solution of 2-methyl-3-nitroanisole (9.96 g, 60 mmol) and tris(dimethylamino)methane (15.5 mL, 89 mmol) in dimethylformamide (30 mL) was heated at 115°C under nitrogen for 3 h. After cooling to ambient temperature a solution of semicarbazide hydrochloride (6.98 g, 63 mmol) and concentrated hydrochloric acid (5.3 mL) in water (75 mL) was added dropwise with vigorous stirring. The mixture was cooled further in an ice bath and the precipitate filtered, rinsed with ice water followed by, in sequence, cold 50% aqueous ethanol, cold ethanol, and ether, then dried to give a semicarbazone. The semicarbazone was suspended with 10% palladium on carbon (3 g) in ethanol (120 mL) in a Parr shaker and placed under a hydrogen atmosphere (50 psi) for 16 h. The mixture was

filtered through Celite and concentrated *in vacuo*. The residue was triturated with ice water, filtered and dried to give the title compound.

5. 4-Benzylxy-1H-indole

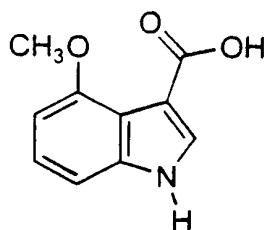


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A solution of 2-nitro-6-benzylxytoluene (13.0 g, 53 mmol) and tris(dimethylamino)methane (13.9 mL, 80 mmol) in dimethylformamide (30 mL) was heated at 115°C under Nitrogen for 3 h. Upon cooling to ambient temperature, a solution of semicarbazide hydrochloride (6.26 g, 56 mmol) and concentrated hydrochloric acid (4.8 mL) in water (70 mL) was added dropwise with vigorous stirring. Ethanol (25 mL) was added and the heterogeneous mixture stirred for 2 h. After cooling in an ice bath, the precipitate was filtered, rinsed with, in sequence, ice water, cold 50% aqueous ethanol, cold ethanol, then ether and dried to give a semicarbazone. A slurry of this semicarbazone (17.64 g, 54 mmol), Raney nickel (18 g of a 50% aqueous slurry) in 1:1 tetrahydrofuran:methanol (145 mL) was heated to 55°C. Hydrazine monohydrate was added in four equal portions (2.7 mL each) at 0.5 h intervals. The mixture was cooled, then filtered through a small pad of silica gel using ether. The filtrate was dried over magnesium sulfate, filtered, concentrated *in vacuo*, and the residue purified by flash chromatography to afford 4-benzylxy-1H-indole as a low melting solid.

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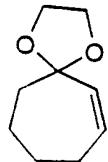
6a. 4-Methoxy-1H-indole-3-carboxylic acid



To a solution of 4-methoxy-1H-indole (7.15 g, 49 mmol) and pyridine (19.7 mL, 243 mmol) in dichloromethane (50 mL) at 0°C under nitrogen was added dropwise a solution of trichloroacetyl chloride (27.1 mL, 243 mmol) in dichloromethane (50 mL). After stirring at 5 0°C for an additional 1.5 h, the mixture was concentrated *in vacuo*. The residue was taken up in the minimal volume of methanol necessary and placed in a freezer overnight. The precipitate was filtered, rinsed well with methanol, and dried to yield 4-methoxy-3-trichloroacetyl-1H-indole. To a stirring solution of sodium methoxide (3.5 mL of a 25 weight % solution in methanol) in methanol (200 mL) at ambient temperature was added 4-methoxy-10 3-trichloroacetyl-1H-indole (9.07 g, 31.0 mmol) in portions over 0.75 h. After stirring an additional 0.75 h, the mixture was cooled in an ice bath, diluted with ice water, acidified with concentrated hydrochloric acid, and the methanol removed *in vacuo*. The resulting heterogeneous mixture was cooled in an ice bath, the precipitate filtered, rinsed with water, and dried to afford methyl 4-methoxy-1H-indole-3-carboxylic ester. A slurry of this ester 15 (5.6 g 27 mmol) in 50% aqueous sodium hydroxide (50 mL) and methanol (50 mL) was stirred at ambient temperature for 19 h. The mixture was cooled in an ice bath, acidified with concentrated hydrochloric acid, the precipitate filtered, rinsed with ice water, and dried to afford 4-methoxy-1H-indole-3-carboxylic acid.

20 **6b.** 4-Benzylxy-1H-indole-3-carboxylic acid was prepped in the same manner as 4-methoxy-1H-indole-3-carboxylic acid in 6a above.

7. 2-Cycloheptenone ethylene ketal



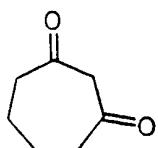
25 Bromine (44.8 g, 0.28 mol) was added dropwise to a stirred solution of cycloheptanone (28.5 g, 0.25 mol) in a 1:1 solution (300 mL) of ethylene glycol and
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tetrahydrofuran at room temperature. The mixture was stirred for 5 hours, then poured into aqueous sodium bicarbonate and extracted 3X with diethyl ether. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 2-bromocycloheptanone ethylene ketal(60 g). A mixture of this crude bromo ketal and a methanolic solution of sodium methoxide (250 mL, 25 wt. % solution) was heated at reflux overnight. The mixture was cooled to ambient temperature, poured into water, and extracted with hexanes. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-cycloheptenone ethylene ketal (39 g).

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8. 1,3-Cycloheptadione



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Mercury (II) acetate (80.7 g, 0.25 mol) was dissolved in water (150 mL), then tetrahydrofuran (150 mL) was added to give a suspension. To this stirring suspension was added 2-cycloheptenone ethylene ketal (39 g, 0.25 mol). After stirring at ambient temperature for 3 hours, the mixture was cooled in an ice water bath. A 10% aqueous sodium hydroxide solution (150 mL) was added, followed by a solution of sodium borohydride (4.8 g, 0.13 mol) in 10% aqueous sodium hydroxide (150 mL). The mixture was allowed to reach ambient temperature and stirred overnight. The mixture was saturated with sodium chloride, stirred for 30 minutes, then allowed to settle; the solution was decanted into brine and extracted with ethyl acetate, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 3-Hydroxycycloheptanone ethylene ketal (36 g).

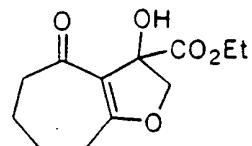
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To a solution of this crude hydroxy ketal and triethylamine (88.3 mL, 0.63 mol) in dichloromethane (250 mL) at 0° C was added, in one portion, sulfur trioxide pyridine complex (98.4 g, 0.63 mol) in methyl sulfoxide (250 mL). The mixture was allowed to ambient temperature, stirred for 1 hour, then cooled in an ice water bath. Brine was added, and the mixture extracted with diethyl ether. The organic layer was washed with aqueous 2N hydrochloric acid then brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 1,3-cycloheptadione *mono* - ethylene ketal (32 g). A solution of this crude ketal in aqueous 2N hydrochloric acid (200 mL) and tetrahydrofuran (200 mL) was stirred at ambient temperature for 20 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate then ⁴²

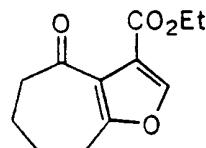
brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 1,3-cycloheptadione (16 g).

9. Ethyl 3-hydroxy-4-oxo-2,3,5,6,7,8-hexahydro-4H-
5 cyclohepta[b]furan-3-carboxylate



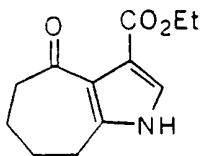
Ethyl bromopyruvate (26 g, 0.13 mol) was added dropwise to a stirred mixture of 1,3-cycloheptadione (16 g, 0.13 mol) and potassium carbonate (35 g, 0.25 mol) in dichloromethane (200 mL). After stirring overnight at ambient temperature, the solvent was removed *in vacuo*, diethyl ether was added and the mixture filtered through Celite. The filtrate was concentrated *in vacuo* to give the title compound (17 g).

10. 10. Ethyl 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan-3-carboxylate



15 Methanesulfonyl chloride (9.7 g, 0.08 mol) was added dropwise to a stirring solution of ethyl 3-hydroxy-4-oxo-2,3,5,6,7,8-hexahydro-4H-cyclohepta[b]furan-3-carboxylate (17 g, 0.07 mol) and triethylamine (30 mL, 0.21 mol) in dichloromethane (100 mL) at 0° C. The mixture was allowed to reach ambient temperature, stirred for 2 hours, then poured into water and extracted with dichloromethane. The organic layer was washed sequentially with aqueous 2N sodium hydroxide, saturated aqueous sodium bicarbonate, and brine, then dried over magnesium sulfate, filtered, concentrated *in vacuo*, and purified on Silica gel (1:1 ethyl acetate / hexanes) to give the title compound.

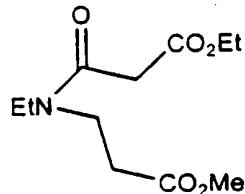
20 11. 4-Oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid



A mixture of ethyl 4-oxo-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan-3-carboxylate (3.48 g, 15.7 mmol) and ammonium acetate (2.41 g, 31.3 mmol) in N,N-dimethylformamide (25 mL) was heated at 115° C for 6 hours. The mixture was concentrated *in vacuo*, ice water was added, and extracted 2X with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate then brine, dried over sodium sulfate, filtered through a small pad of Silica gel (5% methyl alcohol / dichloromethane), and the filtrate concentrated *in vacuo* to give ethyl 4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylate (1.76 g). A solution of this ester in aqueous 5N sodium hydroxide (30 mL) and ethyl alcohol (6 mL) was heated at reflux for 1 hour, then cooled in an ice bath. The mixture was acidified with hydrochloric acid; the resulting precipitate was collected, rinsed with water followed by diethyl ether and allowed to dry to give 4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxylic acid (1.17 g). m.p. 225-227° C.

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12. Ethyl N-ethyl, N-(3-methoxycarbonyl)propyl malonamide

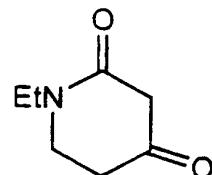


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A solution of methyl acrylate (54 mL, 0.6 mol) in methyl alcohol (500 mL) was added dropwise to a stirred solution of ethylamine (340 mL, 6 mol) in methyl alcohol (1.5 L) at 0° C. After stirring an additional 45 minutes, the mixture was distilled *in vacuo* into one pot, then the solvent removed *in vacuo* (temperature <350° C). To the residue dissolved in dichloromethane (400 mL) at 0° C was added triethylamine (62.5 mL, 448 mmol) followed by a solution of ethyl malonyl chloride (54.4 mL, 427 mmol) in dichloromethane (100 mL). The mixture was stirred for 1 hour, then poured into saturated aqueous ammonium chloride and extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate then water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (87.55 g).

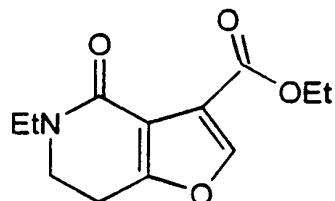
13. N-Ethyl-2,4-piperidione



A solution of ethyl N-ethyl, N-(3-methoxycarbonyl)propyl malonamide (87.55 g, 357 mmol) in methyl alcohol (350 mL) was added dropwise to a methanolic solution of sodium methoxide (25 wt.%, 163 mL) at ambient temperature. After heating at reflux for 1.5 hours, the reaction mixture was allowed to cool and concentrated *in vacuo*. After cooling the residue in an ice water bath, aqueous hydrochloric acid was added and extracted 2X with ethyl acetate, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give N-ethyl-3-methoxycarbonyl-2,4-piperidione (64.4 g). Some of this dione (57 g, 286 mmol) was heated at reflux in a mixture of hydrochloric acid (36 mL) and water (364 mL) for 3.5 hours. After cooling to ambient temperature, the solution was extracted 3X with ethyl acetate, the combined organic layer dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (9.54 g).

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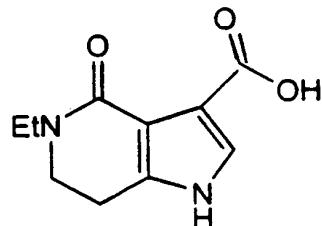
14. Ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydro-furo[3,2-c]pyridine-3-carboxylate



To a stirred solution of potassium hydroxide (3.79 g, 67.6 mmol) in methyl alcohol (15 mL) under Nitrogen at 0°C was added dropwise a solution of N-ethyl-2,4-piperidione (9.54 g, 67.6 mmol) in methyl alcohol (20 mL). The mixture was stirred at 0°C for 1 hour, then a solution of ethyl bromopyruvate (8.9 mL, 71 mmol) in methyl alcohol (50 mL) was added dropwise. After allowing the mixture to stir at ambient temperature for 2.5 hours, a 50% aqueous sodium hydroxide solution (10 mL) was added dropwise and stirring continued an additional 17 hours. After cooling in an ice water bath, the solution was acidified and the methanol removed *in vacuo*. Ice water was added and the precipitate filtered and dried *in*

vacuo to afford 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylic acid (3.91 g). More acid (1.15 g) was obtained via extraction of the aqueous filtrate 2X with ethyl acetate, drying over magnesium sulfate, filtration, concentrating *in vacuo*, and purification on Silica gel (5% methyl alcohol/dichloromethane). A stirring mixture of 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylic acid (4.94 g, 23.6 mmol), potassium carbonate (9.79 g, 70.8 mmol), cesium carbonate (770 mg, 2.4 mmol), and iodoethane (9.4 mL, 118 mmol) in N,N-dimethylformamide was heated at 85° C for 15.5 hours. The reaction mixture was cooled and concentrated *in vacuo*. Ethyl acetate was added, the mixture filtered, the filtrate washed with water, and the organic layer dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound (4.5 g).

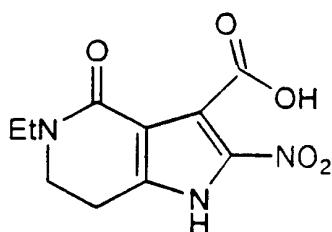
15. 4-Oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid



15 A mixture of ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydrofuro[3,2-c]pyridine-3-carboxylate (3.66 g, 15.4 mmol) and ammonium acetate (5.94 g, 77.1 mmol) in N,N-dimethylformamide (30 mL) was heated at 115° C for 23 hours. The mixture was cooled, concentrated *in vacuo*, ice water added, and the precipitate collected and dried to give ethyl 4-oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylate (1.95 g). The aqueous filtrate was extracted 2X with ethyl acetate, the combined organic layers dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford additional ester (0.68 g). The combined materials were treated with aqueous 5N sodium hydroxide (75 mL) in dioxane (10 mL) at reflux for 2 hours. After cooling in an ice water bath, the mixture was acidified with aqueous hydrochloric acid, and concentrated *in vacuo*. Ethyl acetate was added, the mixture filtered, and the organic layer concentrated *in vacuo*. Trituration with ethyl acetate afforded 4-oxo-5-ethyl-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxylic acid (0.84 g).

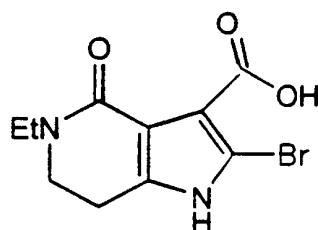
16. 2-Nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid

46



4-Oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol) was added in portions over 30 minutes to fuming nitric acid (2 mL) at 0° C. The mixture was stirred an additional 1.25 hours, then allowed to stir at ambient temperature for 1.25 hours. The mixture was poured into ice water and extracted 2X with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound(0.19 g).

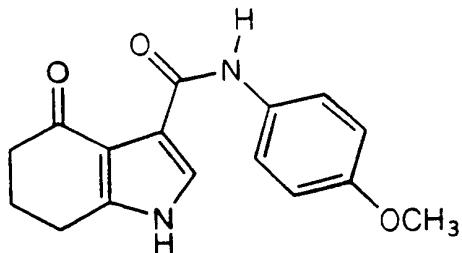
17. 2-Bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid



10

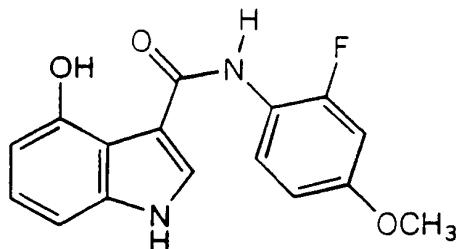
To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (886 mg, 5 mmol) and catalytic benzoyl peroxide in N,N-dimethylformamide (5. mL) at 0° C was added N-bromosuccinimide (1.869 g, 10.5 mmol)in four equal portions over 1 hour. The mixture was stirred an additional hour, then poured into ice water, the precipitate collected and rinsed 15 with water then diethyl ether and dried. Purification on Silica gel (5% methyl alcohol in 1:1:1 dichloromethane/ ethyl acetate/ hexanes) gave 2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (376 mg).

Example 2



Compound 1

A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol),
5 *p*-anisidine (616 mg, 5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride [EDCI] (959 mg, 5 mmol) in 50% aqueous 1,4-dioxane (10 mL) was stirred at
ambient temperature for 17 h. After concentrating *in vacuo*, the residue was taken up in 10%
methanol in ethyl acetate, washed with 1.3M hydrochloric acid then with aqueous sodium
bicarbonate, dried over magnesium sulfate, filtered, and concentrated *in vacuo*.
10 Recrystallization from ethyl acetate afforded N-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-
1H-indole-3-carboxamide (Compound 1); mp 219-220°C.

Example 3

(Compound 2)

5 N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (1.34 g, 3.4 mmol), prepared using the method above, was slurried with 10% palladium on carbon (134 mg) in ethanol (35 mL) in a Parr bottle and placed under a hydrogen atmosphere (50 psi) for 5 h. Methanol (5 ml) was added and the mixture returned to the Hydrogen atmosphere for an additional 18 h. The solution was filtered through Celite, concentrated *in vacuo*, and the residue purified by flash chromatography to afford N-(2-fluoro-4-methoxyphenyl)-4-hydroxy-
10 1H-indole-3-carboxamide (Compound 2) as a beige solid; mp 259-261°C (d).

Example 4

The following compounds were prepared essentially according to the procedures described in Examples 1-3:

15

(a) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 3); mp 217-218°C.

20

(b) N-(4-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 4); mp 259-261°C (d).

(c) N-(3-Ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 5).

25

(d) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 6).

(e) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 7).

(f) N-(4-Methoxyphenyl)-4-methoxy-1H-indole-3-carboxamide (Compound 8).

5 (g) N-(2-Fluoro-4-ethoxyphenyl)-4-methoxy-1H-indole-3-carboxamide
(Compound 9).

(h) N-(4-Cyanophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 10); mp 287-288°C.

10 (i) N-(3-Methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 11); mp 220-223°C.

(j) N-(4-Acetamidophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 12); mp 339-341°C.

15 (k) N-(4-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 13).

20 (l) N-(2-Fluoro-4-methoxyphenyl)-4-benzylxy-1H-indole-3-carboxamide
(Compound 14).

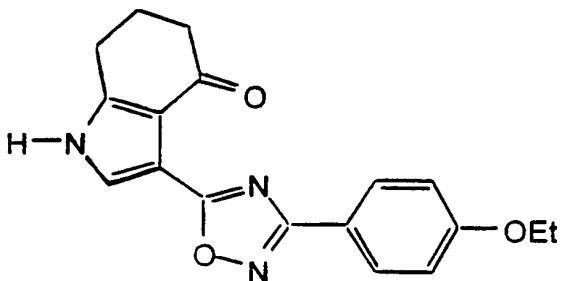
(m) N-(4-Acetylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 15).

25 (n) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 16).

(o) N-(4-Carbomethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 17); mp 261-262°C.

30 (p) N-(4-Carboxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 18).

- (q) N-(4-Ethoxyphenyl)-4-hydroxy-1H-indole-3-carboxamide (Compound 19).
- (r) N-(3-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 20).
- 5 (s) N-(2-Fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide (Compound 21).
- 10 (t) N-(4-Isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 22).
- (u) N-(4-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 23).
- 15 (v) N-(4-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 24).
- (w) N-(4-Aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 25).
- 20 (x) N-(3-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 26); mp: 230-232°C.



- 25 (y) (compound 27)
- (z) N-(2-Fluoro-4-isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 28).

(aa) N-(4-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 29).

5 (ab) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 30); mp 193-194°C.

10 (ac) N-(4-Ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 31).

15 (ad) N-(4-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 32).

20 (ae) N-(2-Methoxy-5-bromophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 33).

(af) N-(3,4-Dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 34).

25 (ag) N-Phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35)
(Also, see Example 5).

(ah) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 36).

25 (ai) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 37), mp 213-215°C.

30 (aj) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 38).

(ak) N-(4-Ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 39).

5 (al) N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 40).

(am) N-(3-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 41).

10 (an) N-(2-Amino-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 42).

(ao) N-(4-Methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 43).

15 (ap) N-Phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 44).

20 (aq) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 45).

(ar) N-(2-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46).

25 (as) N-(3-Fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 47).

(at) N-(2-(4-Hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 48).

30 (au) N-(2-(4-Ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 49).

(av) N-(4-Ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 50) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-ethoxyphenyl)formamide).

5 (aw) N-(2-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 51) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluorophenyl)formamide).

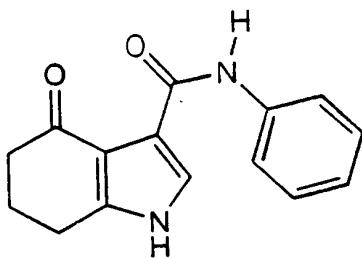
10 (ax) N-Phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 52) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-phenylformamide).

15 (ay) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 53) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-methoxyphenyl)formamide).

(az) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 54) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-ethoxyphenyl)formamide).

20 (ba) N-(4-Fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 55).

Example 5



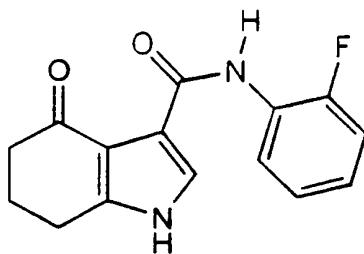
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Compound 35

A mixture of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (179 mg, 1 mmol), aniline (0.46 mL, 5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
54

hydrochloride (959 mg, 5 mmol) in 50% aqueous dioxane (10 mL) was allowed to stir at ambient temperature for 17.5 hours, then concentrated *in vacuo*. The residue was cooled in an ice water bath, aqueous 3.6 N hydrochloric acid was added, and the precipitate collected, rinsed with aqueous 3.6 N hydrochloric acid then water and dried. Recrystallization from ethyl alcohol afforded N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 35) (164 mg). mp 225-226° C.

Example 6

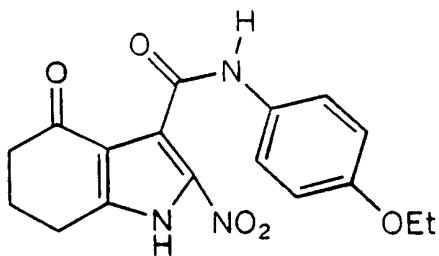


10

Compound 46

To a solution of 4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (538 mg, 3 mmol) and triethylamine (0.88 mL, 6.3 mmol) in N,N-dimethylformamide (15 mL) at 0° C was added ethyl chloroformate (0.57 mL, 6 mmol). After stirring at 0° C for 45 minutes, 2-fluoroaniline (0.58 mL, 6 mmol) was added. The mixture was stirred for an additional 45 minutes, then allowed to stir at ambient temperature for 14 hours. The mixture was poured into aqueous 1.2 N hydrochloric acid and extracted 2X with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. To the residue was added aqueous 1N sodium hydroxide (10 mL) and ethyl alcohol (2 mL) and the mixture heated at reflux for 4.5 hours. After cooling in an ice water bath, the mixture was acidified with aqueous hydrochloric acid, the precipitate collected, rinsed with water and dried. Recrystallization from ethyl alcohol afforded N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 46) (530 mg). mp 238-240° C.

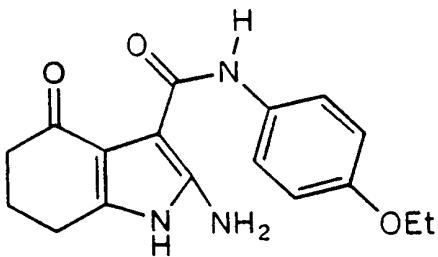
Example 7



(Compound 56)

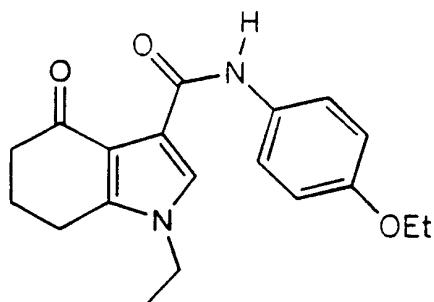
A mixture of 2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxylic acid (0.18 g, 0.8 mmol), *p*-phenetidine (0.52 mL, 4 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (767 mg, 4 mmol) in 50% aqueous dioxane (10 mL) was stirred for 67 hours, then concentrated *in vacuo*. Aqueous 3.6 N hydrochloric acid was added, the mixture cooled in an ice water bath, and the precipitate collected, rinsed with water then diethyl ether, and dried. Purification on Silica gel (10% methyl alcohol/dichloromethane) gave N-(4-ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 56) (51 mg).

Example 8



(Compound 57)

N-(4-Ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (41 mg) was treated with 10% palladium on carbon (5 mg) in ethyl alcohol (10 mL) under hydrogen (50 PSI) in a Parr bottle for 1 hour. The mixture was filtered through Celite, concentrated *in vacuo*, and purified on Silica gel (5% methyl alcohol/dichloromethane) to afford N-(4-ethoxyphenyl)-2-amino-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 57) (12 mg).

Example 9

(Compound 58)

A mixture of N-(4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (204 mg, 0.7 mmol), potassium carbonate (188 mg, 1.4 mmol), cesium carbonate (22 mg, 0.1 mmol), and iodoethane (0.08 mL, 1 mmol) in N,N-dimethylformamide was heated at 85° C for 1 hour. The mixture was cooled and filtered using ethyl acetate. The solid was set aside; the organic layer was washed with water, dried over magnesium sulfate, filtered, concentrated *in vacuo*, and triturated with diethyl ether to give N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (73 mg). The set-aside solid was slurried in aqueous hydrochloric acid, the precipitate collected, rinsed with water and dried to give additional amide (Compound 58) (94 mg). mp. 209-210° C.

Example 10

The following compounds are prepared essentially according to the procedures described in Examples 1-9:

(a) N-(3-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 59); mp 235-237° C.

(b) N-(4-Fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 60); mp 259-261° C.

(c) N-(2-Hydroxy-4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 61); mp 252-254° C.

(d) N-(2-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 62); mp 215-216° C.

5 (e) N-(4-Hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 63); mp 313-315° C.

(f) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 64); mp 335-338 ° C (d).

10 (g) N-(3,4-Dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 65).

(h) N-(3-Hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 66 mp 328-331° C (d).

15 (i) N-(3-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 67); mp 227-228 ° C.

20 (j) N-(2-Fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 68); mp 216-217 ° C.

(k) N-(3-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 69).

25 (l) N-(2-Fluoro-5-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 70); mp 223-225° C.

(m) N-(4-Methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide
(Compound 71); mp 220-222° C.

30 (n) N-(2-Fluoro-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-
carboxamide (Compound 72); mp 181-183° C.
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(o) N-(2-Hydroxy-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 73); mp 238-240° C.

5 (p) N-[4-(Methylamino)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 74); mp 242-244° C.

(q) N-(4-Aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 75); mp 207-210° C.

10 (r) N-(3-Chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 76).

(s) N-(2-Hydroxy-4-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 77); mp 190-195° C.

(t) N-(4-Ethoxyphenyl)-2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 78).

20 (u) N-(4-Ethoxyphenyl)-2-chloro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 79).

(v) N-Phenyl-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 80); mp 248-251 ° C.

25 (w) N-(2-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 81); mp 214-216° C.

(x) N-(3-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 82); mp 247-249° C.

(y) N-(4-Fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 83). *59*

(z) N-(3-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 84).

5 (aa) N-(3-Methylphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 85); mp 233-234° C.

(ab) N-(4-Hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 86); mp 301-303° C.

10 (ac) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 87); mp 340° C.

15 (ad) N-(4-Methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 88).

(ae) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 89).

20 (af) N-(4-Ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 90).

(ag) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 91); mp 178-180° C.

25 (ah) N-Phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 92); mp 218-219° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-phenylformamide).

30 (ai) N-(2-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 93) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluorophenyl)formamide).

(aj) N-(3-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 94) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(3-fluorophenyl)formamide).

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(ak) N-(4-Fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 95) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-fluorophenyl)formamide).

10

(al) N-(3-Methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 96); mp 190 °C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(3-methoxyphenyl)formamide).

15

(am) N-(4-Hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 97); mp 278-280° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-hydroxyphenyl)formamide).

20

(an) N-(4-Methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 98); mp 178-179 ° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-methoxyphenyl)formamide).

25

(ao) N-(4-Ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 99); mp 198-201° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(4-ethoxyphenyl)formamide).

30

(ap) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 100); mp 158-159 ° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-methoxyphenyl)formamide).

(aq) N-(2-Fluoro-4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 101); mp 305-308° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-hydroxyphenyl)formamide).

5

(ar) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 102); mp 172-174° C (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-4-ethoxyphenyl)formamide).

10

(as) N-(2-Fluoro-5-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide (Compound 103) (alternate name: (10-aza-6-oxobicyclo[5.3.0]deca-1(7),8-dien-8-yl)-N-(2-fluoro-5-methoxyphenyl)formamide).

15

(at) N-(2-Fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 104); mp 150-152 °C.

(au) N-(4-Ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 105); mp 145-147° C.

20

(av) N-(2-Fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide (Compound 106); mp 154-155° C.

(aw) N-(4-Ethoxyphenyl)-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 107); mp 215-216° C.

25

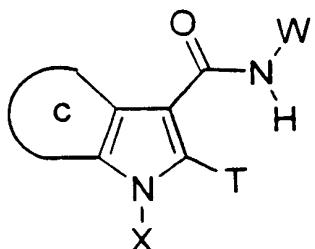
(ax) N-(4-Ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 108); mp 209-210° C.

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims.

To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

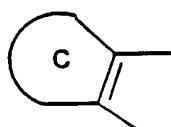
WHAT IS CLAIMED IS:

1. A compound of the formula:

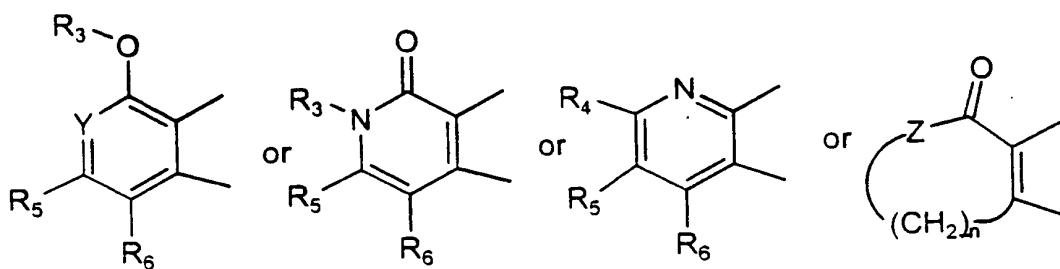


or the pharmaceutically acceptable non-toxic salts thereof wherein:

- 5 T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;
- X is hydrogen, hydroxyl or lower alkyl;
- 10 W is phenyl or phenylalkyl where each alkyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and



15 represents



wherein:

Y represents nitrogen or C-R₄;

represents N-R₇ or a carbon atom substituted with R₈ and R₉;

n is 1, 2, 3, or 4;

R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

R₄ is halogen or trifluoromethyl; or

5 -OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

10 -CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl;

R₅ and R₆ are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy;

15 R₇ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

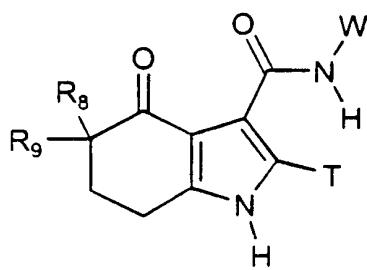
R₈ is hydrogen or lower alkyl; and

R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

20 R₉ is -CONR₁₄R₁₅ or -(CH₂)_kNR₁₄R₁₅, where k is 0, 1, or 2; R₁₄ represents hydrogen, lower alkyl; and R₁₅ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholyl, piperidyl, pyrrolidyl, or N-alkyl piperazyl.

25

2. A compound of the formula:



65

or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

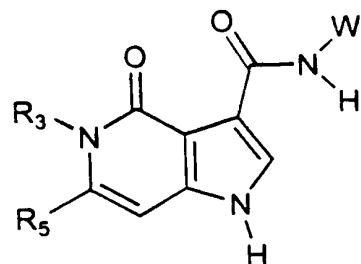
T is halogen, hydrogen, hydroxy, nitro, amino or lower alkoxy;

10 R₈ is hydrogen or lower alkyl; and

R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

15 R₉ is -CONR₁₄R₁₅ or -(CH₂)_kNR₁₄R₁₅, where k is 0, 1, or 2; R₁₄ represents hydrogen, lower alkyl; and R₁₅ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₄R₁₅ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl.

3. A compound of the formula:

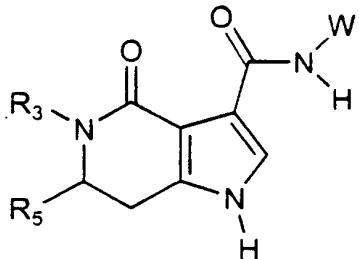


20 or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; and
R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

5 4. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

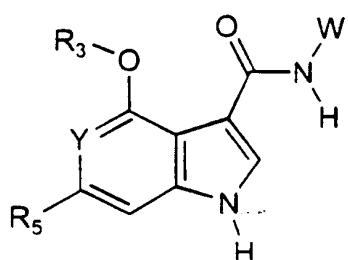
W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7

10 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

15 R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

5. A compound of the formula:



20 or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7

carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

5 R₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl;

Y is nitrogen or C-R₄;

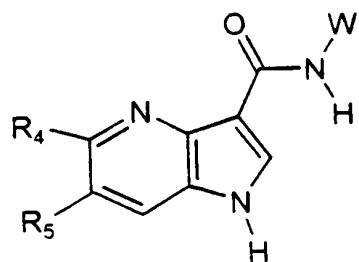
R₄ is halogen or trifluoromethyl; or

10 R₄ is -OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

R₄ is -CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; and

15 R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

20 6. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

W is phenyl or phenylalkyl where each phenyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkyleneedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₄ is halogen or trifluoromethyl; or

R₄ is -OR₁₀, -COR₁₀, -CO₂R₁₀, -OCOR₁₀, or -R₁₀, where R₁₀ is hydrogen, phenyl, 2-, 3-, 5 or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

R₄ is -CONR₁₁R₁₂ or -(CH₂)_mNR₁₁R₁₂, where m is 0, 1, or 2; R₁₁ represents hydrogen, lower alkyl; and R₁₂ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or NR₁₁R₁₂ 10 forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; and

R₅ is hydrogen, halogen, lower alkyl, or lower alkoxy.

7. A compound according to claim 1, which is N-(3-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

8. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-benzyloxy-1H-indole-3-carboxamide.

20 9. A compound according to claim 1, which is N-(4-isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

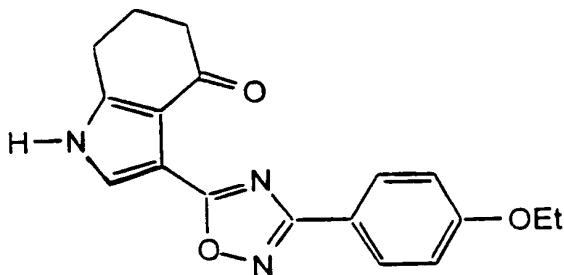
10. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 11. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

12. A compound according to claim 1, which is N-(4-aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 13. A compound according to claim 1, which is N-(3-fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

14. A compound according to claim 1, which is



5 15. A compound according to claim 1, which is N-(2-fluoro-4-isopropoxypyhenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 16. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 17. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 18. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

19. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 20. A compound according to claim 1, which is N-(2-methoxy-5-bromophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

21. A compound according to claim 1, which is N-(3,4-dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 22. A compound according to claim 1, which is N-phenyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

23. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

24. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.
5

25. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 26. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

27. A compound according to claim 1, which is N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 28. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 29. A compound according to claim 1, which is N-(2-amino-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30. A compound according to claim 1, which is N-(4-methylaminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 31. A compound according to claim 1, which is N-phenyl-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 32. A compound according to claim 1, which is N-(3-hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide (Compound 45)

33. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

34. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 35. A compound according to claim 1, which is N-(2-(4-hydroxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

36. A compound according to claim 1, which is N-(2-(4-ethoxyphenyl)ethyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 37. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

38. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

15 39. A compound according to claim 1, which is N-phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

20 40. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

41. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

25 42. A compound according to claim 1, which is N-(4-fluoro-2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

43. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 44. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-nitro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

45. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-amino-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 46. A compound according to claim 1, which is N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

47. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 48. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

49. A compound according to claim 1, which is N-(2-hydroxy-4-fluorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 50. A compound according to claim 1, which is N-(2-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 51. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

52. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 53. A compound according to claim 1, which is N-(3,4-dihydroxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

54. A compound according to claim 1, which is N-(3-hydroxy-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 55. A compound according to claim 1, which is N-(3-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

56. A compound according to claim 1, which is N-(2-fluoro-4-isopropoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

57. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

58. A compound according to claim 1, which is N-(2-fluoro-5-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 59. A compound according to claim 1, which is N-(4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

60. A compound according to claim 1, which is N-(2-fluoro-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 61. A compound according to claim 1, which is N-(2-hydroxy-4-methylphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 62. A compound according to claim 1, which is N-[4-(methylamino)phenyl]-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

63. A compound according to claim 1, which is N-(4-aminophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 64. A compound according to claim 1, which is N-(3-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

65. A compound according to claim 1, which is N-(2-hydroxy-4-chlorophenyl)-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 66. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-bromo-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

67. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-chloro-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

5 68. A compound according to claim 1, which is N-phenyl-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

69. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

10 70. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

71. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

15 72. A compound according to claim 1, which is N-(3-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

20 73. A compound according to claim 1, which is N-(3-methylphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

74. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

25 75. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

76. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

30 77. A compound according to claim 1, which is N-(2-fluoro-5-methoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

78. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

79. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-5,5-dimethyl-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.
5

80. A compound according to claim 1, which is N-phenyl-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

10 81. A compound according to claim 1, which is N-(2-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

82. A compound according to claim 1, which is N-(3-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.
15

83. A compound according to claim 1, which is N-(4-fluorophenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

20 84. A compound according to claim 1, which is N-(3-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

85. A compound according to claim 1, which is N-(4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.
25

86. A compound according to claim 1, which is N-(4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

87. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.
30

88. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

89. A compound according to claim 1, which is N-(2-fluoro-4-hydroxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

90. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

91. A compound according to claim 1, which is N-(2-fluoro-5-methoxyphenyl)-4-oxo-1,4,5,6,7,8-hexahydro-cyclohepta[b]pyrrole-3-carboxamide.

92. A compound according to claim 1, which is N-(2-fluoro-4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

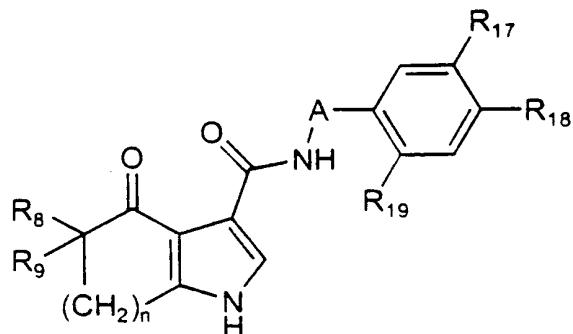
93. A compound according to claim 1, which is N-(4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

94. A compound according to claim 1, which is N-(2-fluoro-4-ethoxyphenyl)-4-oxo-4,5,6,7-tetrahydro-1H-pyrrolo[3,2-c]pyridine-3-carboxamide.

95. A compound according to claim 1, which is N-(4-ethoxyphenyl)-2-methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

96. A compound according to claim 1, which is N-(4-ethoxyphenyl)-1-ethyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-3-carboxamide.

97. A compound of the formula:



wherein:

R₈ and R₉ are independently alkyl or hydrogen;

A represents an alkylene group of 1-6 carbon atoms optionally substituted with up to two alkyl groups independently having 1-3 carbon atoms;

n is 1 or 2;

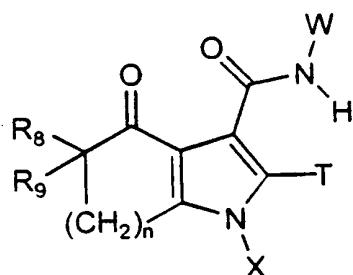
5 R₁₇ is hydrogen, halogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl having 1-6 carbon atoms;

R₁₈ is hydrogen, hydroxyl, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl is independently straight or branched chain lower alkyl, NR₁COR₂, COR₂,

10 CO₂R₂ where R₁ and R₂ are as defined above, cyano, or halogen; and

R₁₉ is hydrogen, hydroxyl, or halogen.

98. A compound of the formula:



15 wherein

W is phenyl or phenylalkyl where each alkyl is optionally substituted with up to 5 groups independently selected from halogen, hydroxy, lower alkyl, cycloalkyl having 3-7 carbon atoms, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or cycloalkyl having 3-7 carbon atoms, lower alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, alkylenedioxy, or NR₁COR₂, COR₂, or CONR₁R₂ where R₁ and R₂ are the same or different and represent hydrogen, lower alkyl or cycloalkyl having 3-7 carbon atoms; and

R₈ is hydrogen or lower alkyl; and

25 R₉ is -COR₁₃, -CO₂R₁₃ or -R₁₃, where R₁₃ is hydrogen, phenyl, 2-, 3-, or 4-pyridyl, lower alkyl, or phenylalkyl or 2-, 3-, or 4-pyridylalkyl where each alkyl is lower alkyl; or

T represents hydrogen, amino, or nitro;

X is alkyl or hydrogen; and

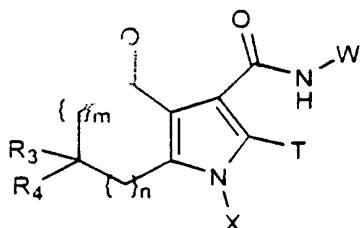
n is 1 or 2.

- 5 99. A compound according to claim 98, wherein
 R₈ and R₉ are independently alkyl or hydrogen;
 X and T are hydrogen;
 W is phenyl optionally substituted with up to two groups selected from halogen, hydroxy,
 lower alkyl, amino, mono- or dialkylamino where each alkyl is independently lower alkyl or
 10 cycloalkyl having 3-7 carbon atoms, and lower alkoxy;
 and n is 2.

100. A compound according to claim 99, wherein W is phenyl mono- or
 disubstituted with a substituent selected from halogen and alkoxy.

- 15 101. A compound according to claim 97, wherein n is 2.

102. A compound of the formula:



- 20 or the pharmaceutically acceptable non-toxic salts thereof wherein:
 W is aryl or heteroaryl, each of which is optionally substituted with up to five groups selected
 independently from
 halogen, cyano, hydroxy, alkyl or cycloalkyl having 3-7 carbon atoms,
 amino or mono- or dialkylamino where each alkyl is independently lower alkyl or
 25 cycloalkyl having 3-7 carbon atoms,
 alkoxy or cycloalkyl alkoxy having 3-7 carbon atoms, or
 NR₁COR₂, COR₂, CONR₁R₂ or CO₂R₂ where R₁ and R₂ are the same or different
 and represent hydrogen or alkyl or cycloalkyl having 3-7 carbon atoms; and
 T is halogen, hydrogen, hydroxyl, amino or alkoxy;

X is hydrogen, hydroxyl or alkyl;

m is 0, 1, or 2;

n is 0, 1, or 2; and

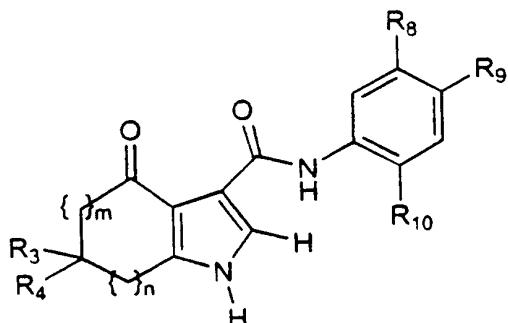
R₃ and R₄ are the same or different and represent hydrogen, alkyl, COR₅ or CO₂R₅ where

5 R₅ is alkyl or cycloalkyl having 3-7 carbon atoms, CONR₆R₇ where R₆ and R₇ are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms, phenyl, 2-,3-, or 4-pyridyl , or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms.

10

103. A compound of the formula:



wherein

R₃ and R₄ are the same or different and represent hydrogen, alkyl, COR₅ or CO₂R₅ where

15 R₅ is alkyl or cycloalkyl having 3-7 carbon atoms, CONR₆R₇ where R₆ and R₇ are selected independently from hydrogen, alkyl, cycloalkyl having 3-7 carbon atoms, phenyl, 2-,3-, or 4-pyridyl , or NR₆R₇ forms a heterocyclic group which is morpholinyl, piperidinyl, pyrrolidinyl, or N-alkyl piperazinyl; or

R₃-R₄ together represent a cyclic moiety having 3-7 carbon atoms;

20 R₈ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino; and

R₉ is hydrogen, halogen, cyano, hydroxy, alkyl, alkoxy, cycloalkyl alkoxy having 3-7 carbon atoms, amino, mono- or dialkylamino, NR₁COR₂, COR₂, or CO₂R₂ where R₁ and R₂ are the same or different and represent hydrogen, alkyl, or cycloalkyl having 3-7 carbon atoms; and

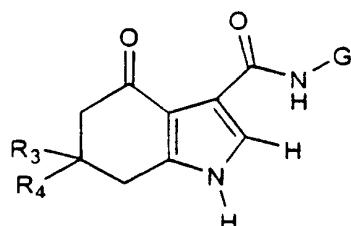
25

R₁₀ is hydrogen, halogen, hydroxyl, alkyl, alkoxy, amino, mono- or dialkylamino;

m is 0, 1, or 2; and

n is 0, 1, or 2.

5 104. A compound of the formula:

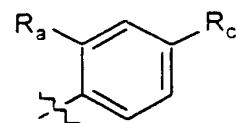
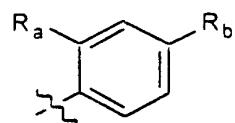
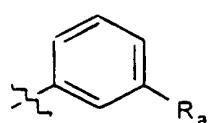
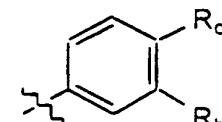
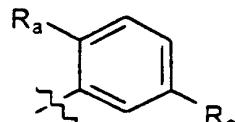
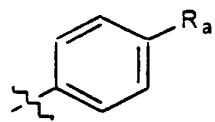
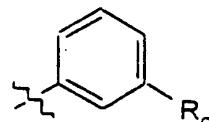
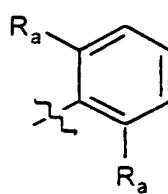
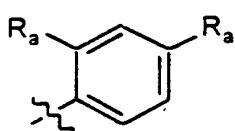
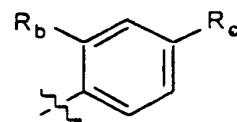
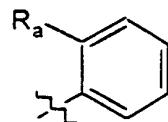
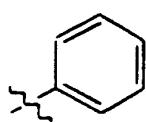


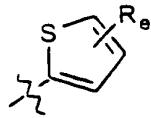
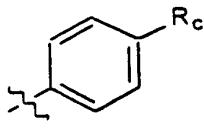
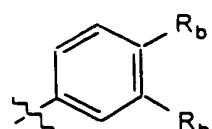
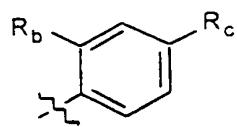
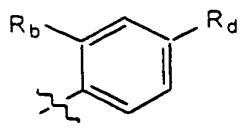
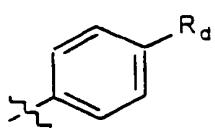
where

G represents thienyl, thiazolyl, pyridyl, napthyridinyl, quinolinyl, or phenyl, each of which is optionally mono-, di- or trisubstituted with halogen, alkyl, alkoxy, or hydroxy; and

10 R₃ and R₄ are the same or different and represent hydrogen or alkyl, provided that not both R₃ and R₄ are hydrogen.

105. A compound according to claim 104, wherein G is selected from the following:





wherein, independently,

R_a is halogen;

R_b is hydroxy;

R_c represents alkoxy;

5 R_d represents alkyl;

R_e represents hydrogen or R_d;

R_f represents hydrogen, or R_c; and

R_g represents hydrogen, R_a or R_c.

10 106. A compound according to claim 105, wherein R_a groups in G are fluorine; R_c groups in G are methoxy and ethoxy; and R_d groups in G are methyl and ethyl.

INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/US 97/12153

A. CLASSIFICATION OF SUBJECT MATTER				
IPC 6	C07D209/42	C07D413/04	C07D209/52	A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 11885 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); HUTCHISON ALAN (US)) 4 May 1995 see the whole document ---	1-106
E	WO 97 26243 A (NEUROGEN CORP ;ALBAUGH PAMELA (US); LIU GANG (US); SHAW KENNETH (U) 24 July 1997 see the whole document -----	1-106



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1997	15.10.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer De Jong, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/12153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511885 A	04-05-95	US 5484944 A AU 8126594 A CA 2175204 A CN 1143953 A CZ 9601129 A EP 0725775 A FI 961776 A HU 76064 A NO 961655 A PL 314136 A SE 9601563 A US 5608079 A	16-01-96 22-05-95 11-05-95 26-02-97 16-04-97 14-08-96 14-06-96 30-06-97 10-06-96 19-08-96 22-05-96 04-03-97
WO 9726243 A	24-07-97	NONE	